UNIVERSITY OF ALBERTA

SEQUENTIAL USE OF THE DIELS-ALDER REACTION AND RADICAL CYCLIZATION FOR THE CONSTRUCTION OF POLYCYCLIC COMPOUNDS

by

RAYMOND JOHN BERGSTRA

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DEPARTMENT OF CHEMISTRY

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Dr. G. Kotovych .....George Kotovych.....
Dr. P. Sporns .....Peter Sporns.....
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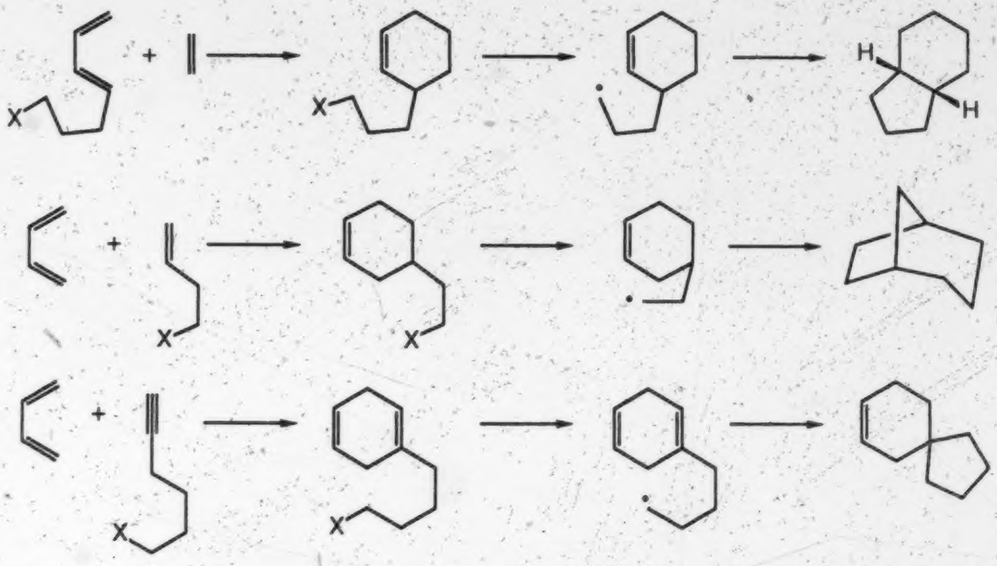
Date: Nov 23, 1990

To my wife and family

ABSTRACT

This thesis describes the development of a synthetic methodology involving the use of the Diels-Alder reaction in conjunction with radical cyclization.

The intermolecular Diels-Alder reaction, in which either the diene or the dienophile carries a suitably located homolyzable substituent (**X**), such as a phenylseleno group, represents a convenient method for assembly of compounds that can undergo radical cyclization (see Scheme).



The technique can be used to generate polycyclic structures that are fused in a linear, bridged, or spiro manner. The hetero Diels-Alder version is equally versatile

in this connection. The method was used in a short, formal synthesis of an indolizidine alkaloid.

The second section deals with an investigation of the effects of electron withdrawing groups on a double bond with respect to the regiochemistry of radical cyclization. It was found that a sufficiently strong electron withdrawing group can induce an *endo* cyclization, via Michael addition of the radical.

ACKNOWLEDGEMENTS

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LIST OF ABREVIATIONS

Ac	acetyl
AIBN	azoisobutyronitrile
Ar	aryl
Bn	benzyl
Bz	benzoyl
tBu	tertiary butyl
DBU	diazabicycloundecene
DCC	dicyclohexylcarbodiimide
DDQ	dichlorodicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
HMDS	hexamethyldisilane
Im	imidazole
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MCPBA	*meta*-chloroperbenzoic acid
MOM	methoxymethyl
NBS	*N*-bromosuccinimde
Ph	phenyl
PTS	*para*-toluenesulfonyl
pyr	pyridine
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine

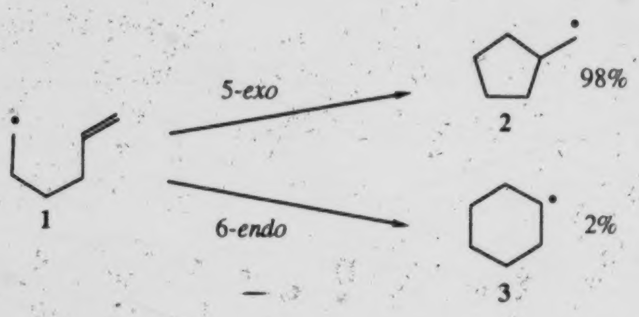
I. INTRODUCTION

In recent years there has been a remarkable number of publications dealing with the formation of carbon-carbon bonds using radical reactions. This interest is due to the fact that these reactions are conducted under very mild conditions and in the presence of a wide variety of functionalities. One aspect of radical chemistry is the intramolecular reaction, in which case the product is a cyclic compound. In light of the large number of naturally occurring compounds that contain a cyclic unit, this process has become a particularly important one to the organic chemist for the synthesis of natural products.

The earliest examples of radical cyclization were given by Julia[1] in 1964. However, the process did not attract wide usage due to the paucity of techniques available for the generation of free radicals. This limitation has since been overcome, as shown by recent comprehensive reviews[2] on the general subject of radicals in organic chemistry. Subsequently, the bounds for synthetic applications of radical cyclization are no longer the generation of the radical, but rather, the construction of the molecular framework that is conducive to cyclization. In other words, the methodology involves two steps, the first being the coupling of a radical source and a radical acceptor, and the second being the cyclization itself. This review will present an account of the basic chemical principles involved in radical cyclization, followed by applications to synthesis. The synthetic applications will be categorized by the type of methodology used to assemble the cyclization precursor. Particular emphasis will be placed on the formation of five- and six-membered rings, since these are the most common ring sizes found in natural products.

PRINCIPLES OF RADICAL CYCLIZATION

The most commonly used system ~~in~~ radical cyclization is the ring closure of the 5-hexenyl radical **1** (eq. 1).[3] Although there are two modes of cyclization possible, the 5-*exo* and the 6-*endo*, and both are allowed by Baldwin's rules,[4] the 5-*exo* process is favoured. It should be noted that the outcome of 5-*exo* closure is the formation of a primary radical **2**, as opposed to the thermodynamically more favourable secondary radical **3** formed by 6-*endo* closure.



eq. 1

Since this initial surprising observation, the behaviour of the 5-hexenyl radical has been extensively studied, and it is now accepted that, due to the extremely high reactivity of the radical, the reaction is under kinetic control. This implies that the transition state is early along the reaction coordinate and is reactant-like. Therefore, the stability of the product is not a factor and the explanation for the preference for 5-*exo* closure is rationalized in terms of stereoelectronic effects.

The transition state involves overlap of the singly occupied molecular orbital (SOMO) of the radical, with the lowest unoccupied molecular orbital (LUMO) of the the olefin. Therefore, the geometry of the LUMO dictates the preferred direction of approach of the radical and consequently, the shape of the transition state for optimum overlap of the SOMO and the LUMO (Fig. 1).

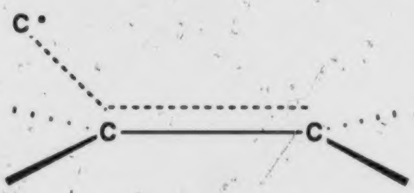


Fig. 1 Transition state for radical addition

Beckwith[5] has shown by calculations and molecular modeling, that this interaction is best accommodated in the 5-*exo* case (Fig. 2), and he has given the relative rates of ring closure of a variety of 5-hexenyl radicals (Table 1).

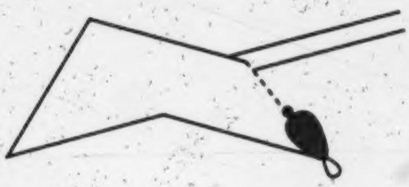
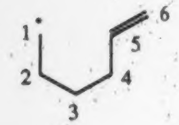
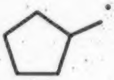
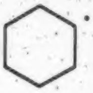
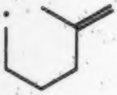
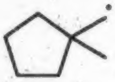
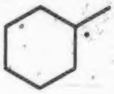
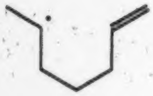
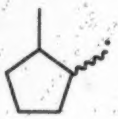
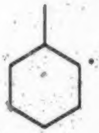
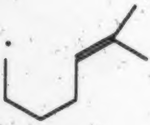
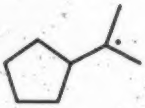
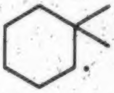
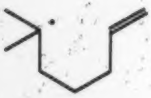
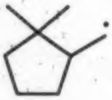
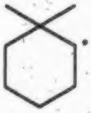


Fig. 2 5-*Exo* ring closure

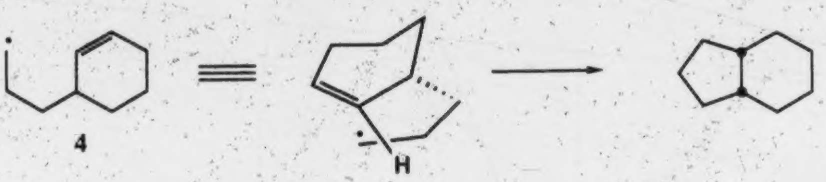
The examples show that in most cases (except entry 2) the rate of 5-*exo* closure is more than 50 times faster than the 6-*endo* process.

TABLE 1

Relative Rates of Radical Ring Closure at 20°C

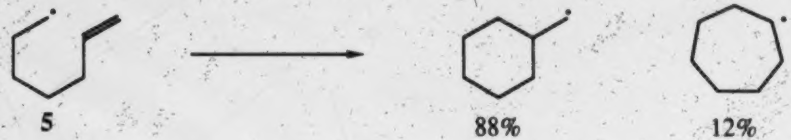
	Starting Radical	Products		k *exo*	k *endo*
1				1	0.02
2				0.022	0.04
3				1.4	0.02
4				2.4	0.011
5				1.52	0.03

The stereoelectronic guidelines that determine the preferred transition state have several significant practical implications for ring-forming reactions using radicals. First of all, it is immediately apparent that the radical cyclization process has its greatest synthetic utility in the synthesis of 5-membered rings. Other processes are allowed, and can be useful, but do suffer some limitations (*vide infra*). Secondly, when the radical trap is contained in a ring, i.e., **4** (eq. 2), and the product would then be bicyclic, there is an overwhelming preference for the *cis*-fused ring geometry.

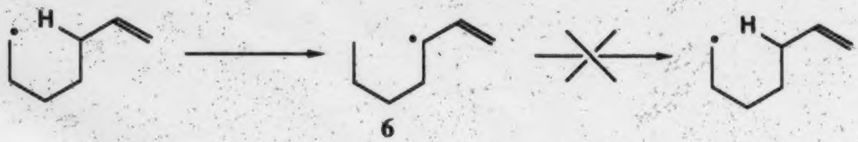


eq. 2

Finally, and of equal importance in synthesis, is the fact that alkyl substitution on the radical-bearing carbon does not retard the reaction rate, but in fact (entry 5) can cause a rate enhancement. Ring closure of the 6-heptenyl radical **5** (eq. 3) is also widely used, but it has limitations. The increase in chain length gives the molecule sufficient flexibility so that the difference between the SOMO-LUMO overlap in the *exo vs endo* transition states is less. The result is a decrease in selectivity.[5] In addition, the reduction product (hydride addition prior to cyclization) is obtained, and this occurs via a 1,5-hydrogen abstraction[6] giving a stable allylic radical **6**, thus terminating the cyclization pathway (eq. 4).

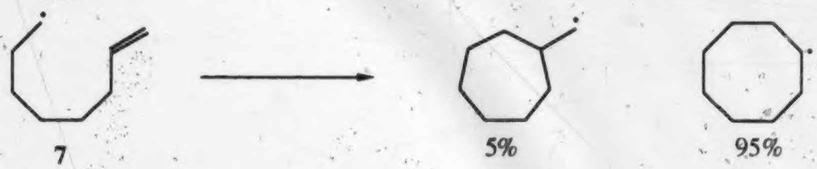


eq. 3



eq. 4

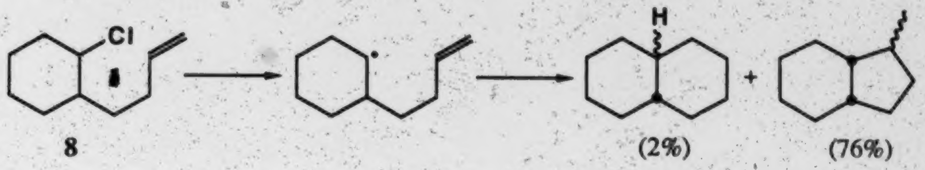
The 7-octenyl radical **7** (eq. 5) prefers the *endo* mode of closure almost exclusively. However, the rate of closure is vastly reduced,[5] and so this process not synthetically useful.



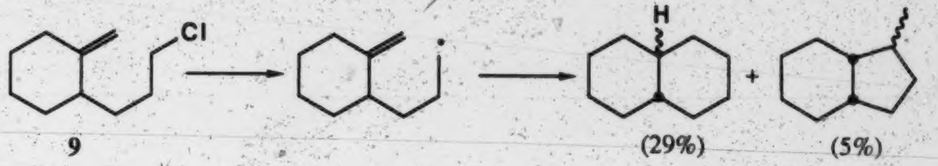
eq. 5

As alluded to earlier, given the inherent preference for the 5-hexenyl radical to form a five membered ring, this is the process most commonly encountered in synthetic organic chemistry (*vide infra*). However, there are factors that can perturb the 5-*exo* mode of cyclization in favour of the 6-*endo* pathway. These factors include substitution on the double bond, the presence of heteroatoms and sp^2 centres in the ring being formed, conformational restrictions due to the presence of other rings in the system, as well as stabilizing groups *alpha* to the radical. In the following examples, the observed phenomena are related, as far as possible, to the accepted stereoelectronic guidelines, i.e., to the fact that the observed ring closure arises from the transition state with optimum SOMO-LUMO overlap. However, in each case there may be several subtle factors involved, and it is often unclear what is the major cause of the regiochemical reversal.

Alkyl substituents on C(5) (Table 1, entry 2) result in an increased production of the 6-*endo* product. It is important to note that this is not due to the preferential formation of a tertiary radical, as the rate of 6-*endo* closure has remained essentially unchanged. It is more likely a relatively simple example of steric inhibition at C(5), as the data show that the rate of the 5-*exo* closure has been greatly reduced relative to the basic 5-hexenyl case. Notwithstanding the early transition state, steric factors can be important when the proximal olefinic carbon is substituted. This phenomenon has been exemplified by Beckwith, and in two contrasting examples, he has shown how one can vary the regiochemical outcome of a 5-hexenyl radical closure (eq. 6,7).[7] Compound **9** is stericly biased in favour of 6-*endo* closure, but the overall yield of cyclized material is low, due to the low rate of both the *exo* and *endo* processes.

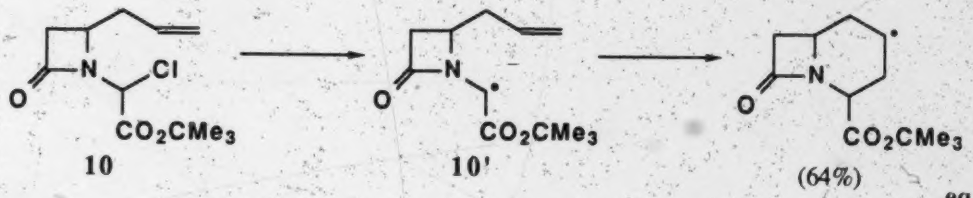


eq. 6

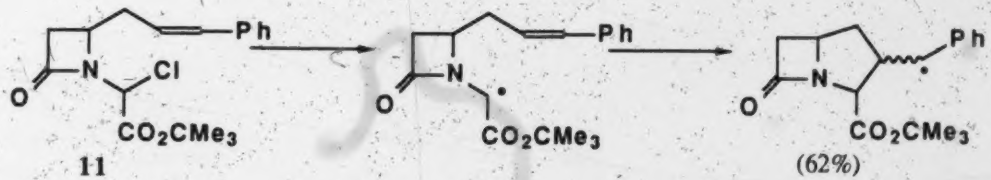


eq. 7

An increase in the amount of 6-*endo* ring closed product has also been observed when the pendants are attached to another ring.[8] Bachi[8a] has shown, in his synthesis of bicyclic β-lactams, that cyclization of compounds such as **10** results in a good yield of 6-*endo* product (eq. 8).


N
Cl
O
CO2CMe3
10
10'
(64%)

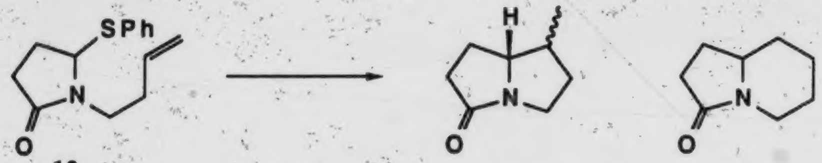
eq. 8


Ph
N
Cl
O
CO2CMe3
11
(62%)

eq. 9

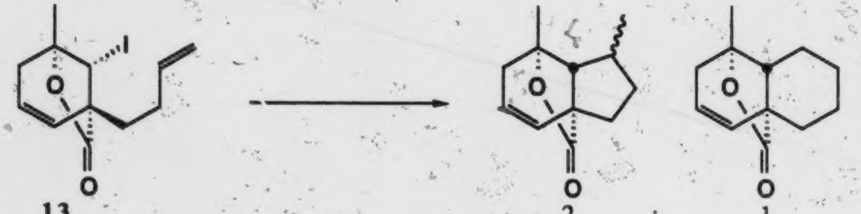
This outcome can be explained by the fact that the presence of the four-membered ring restricts the conformational freedom of **10'**, disfavouring the 5-*exo* transition state (and the formation of a four-five system). There is a balance, however, because substitution on the terminus of the olefin, as in **11**, results in five-membered ring formation only (eq. 9).[8a]

Similar observations have been made in the radical cyclization of δ-lactams, as in the case of **12** (eq. 10).[8b] Radical induced cyclization led to formation of a mixture of five- and six-membered rings.



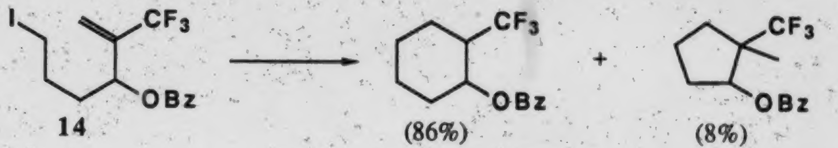
12 2.2 : 1 **eq. 10**

Hart also found that the radical cyclization of bicyclic iodolactone **13**, was not a useful process as a mixture of *exo* and *endo* products was obtained (eq. 11).[8c]

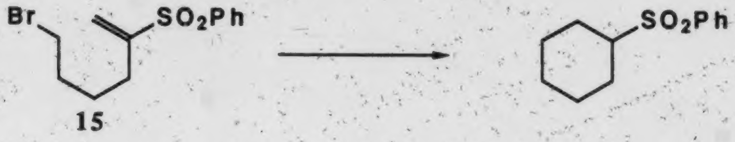


13 2 : 1 **eq. 11**

Electron-withdrawing groups on the olefin are known to activate the *beta* position of the double bond towards radical addition.[9] In this regard, ring closure of the trifluoromethyl substituted olefin **14** resulted in exclusive formation of the six membered ring (eq. 12),[10a] as was also the case with vinyl sulfone **15** (eq. 13).[10b] In each case, cyclization involved a 6-*endo* Michael addition.

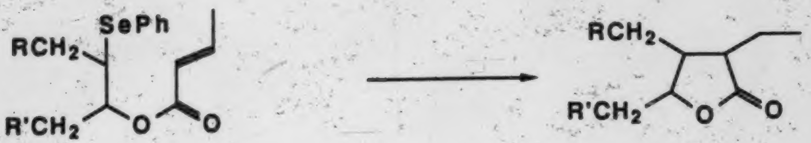


eq. 12



eq. 13

However, as the system becomes more complex, the results are less easy to interpret.[11] For example, in the case of lactone formation using crotonate derivatives as the radical acceptor, Clive[11a] observed cyclization in a 5-*exo* anti-Michael fashion from both cyclic and acyclic starting materials (see **16**, eq. 14). A similar result was obtained by Bowman in the radical cyclization of **17** (eq. 15).[11b] This is especially surprising as the radical formed from **17** closes onto the fully substituted terminus of the olefin.

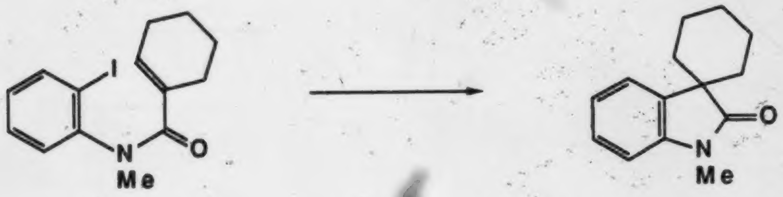


16

R=R'= H, CH_2, $(CH_2)_2$, $(CH_2)_3$

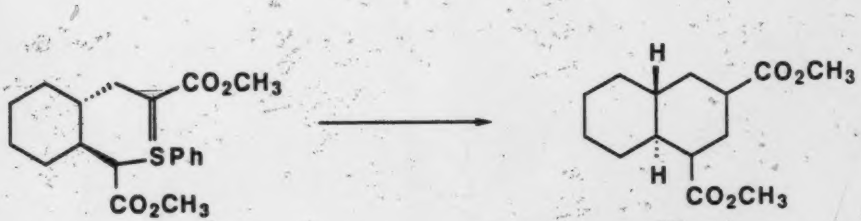
eq. 14

These results are probably related in some, as yet undefined way, to the presence of a hetero atom. It is, for example, known that oxygen in the ring being formed enhances the rate of 5-*exo* closure (*vide infra*). Also noteworthy are results from Posner.[11c] In an all carbon cyclization, he obtained a decalin system **18** via a 6-*endo* Michael process (eq. 16). Here, the 5-*exo* pathway is probably disfavoured by the trans-ring fusion of the resulting product.



17

eq. 15

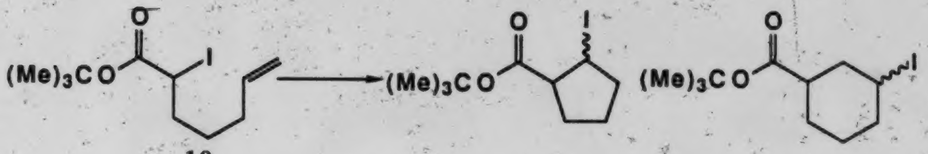


18

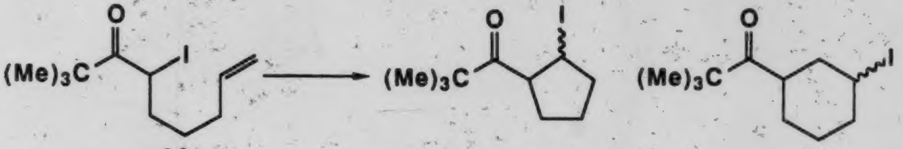
eq. 16

The use of stabilized radicals, even under conditions of irreversible closure, tends to lead to a larger proportion of

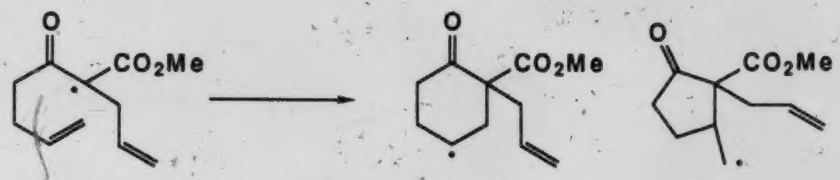
6-*endo* product.[12] Cyclization of carbonyl-stabilized radicals formed from iodides **19** and **20** gave a mixture of products (eq. 17 and 18),[12a] while Snider[12b] showed that doubly stabilized radical **21** led primarily to 6-*endo* cyclization (eq. 19).



19 (69%) (5%) eq. 17



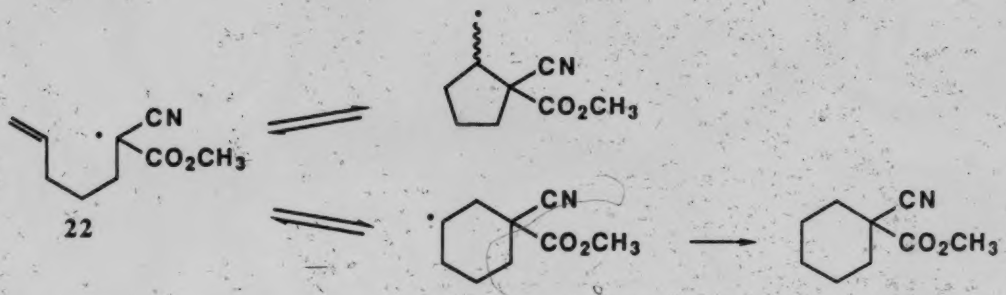
20 (66%) (16%) eq. 18



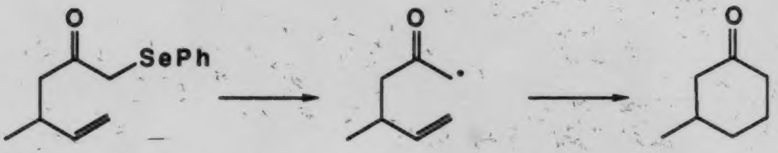
21 (43%) (16%) eq. 19

It is known that at higher reaction temperatures, intramolecular radical additions involving doubly stabilized radicals (see **22**, Scheme 1) can be reversible[1,12c] thus leading to the more stable six-membered ring. These are the early results of Julia, as high reaction temperatures were required in order to generate the radical.

SCHEME 1



In the cyclization of **21** (eq. 19), however, one of the carbonyls is in the ring being formed, and this creates another significant parameter. For example, it has been observed[13a] (in acyclic cases) that α-keto radicals (see **23**, eq. 20) prefer the *endo* mode of cyclization, when the ketone (sp^2 center) is in the ring being formed.



23

eq. 20

A variety of systems similar to **23** were subsequently investigated by Houk,[12b] and it was determined that the decrease in 5-*exo* closure can be attributed to the preferred conformation of the radical relative to the carbonyl. This conformation has the three *p*-orbitals parallel (Fig. 3).

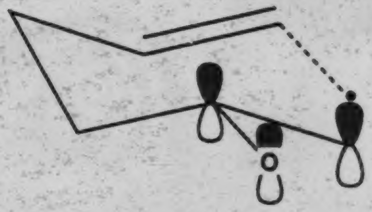
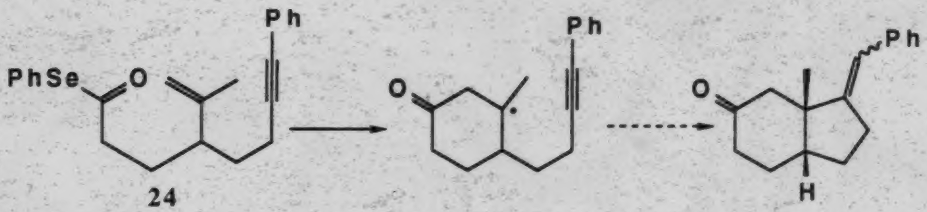


Fig. 3 *Endo* closure of α-keto radical

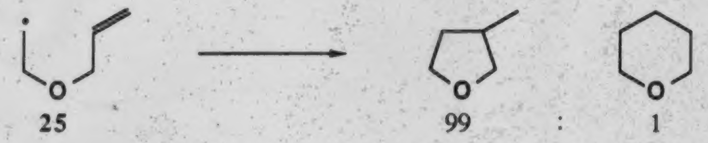
This situation implies the presence of an energy barrier for the rotation of the radical species to adopt the conformation necessary for 5-*exo* closure according to Fig. 2. Therefore the 6-*endo* product is observed.

Acyl radicals generated from selenoesters, i.e., **24**, give exclusively *endo* products (eq. 21).[14] The explanation for this observation is not known for certain, but this result is consistent with that shown in Table 1, entry 2, where substitution on C(5) caused an increase in production of the *endo* product.



eq. 21

The presence of a heteroatom in the ring being formed is known to affect the rates of radical ring closure. For example, the 3-oxa-5-hexenyl system **25**[5] undergoes ring closure 37 times faster than the corresponding hydrocarbon, and there is better selectivity in favour of the 5-*exo* process (eq. 22).



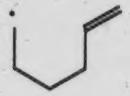
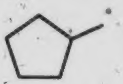
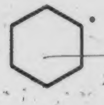
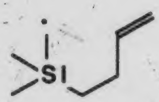
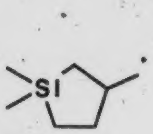
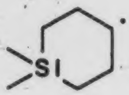
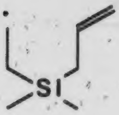
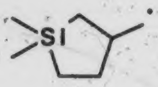
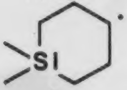
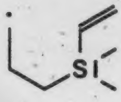
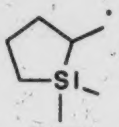
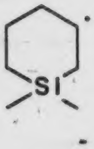
eq. 22

On the other hand, several groups have observed that when silicon is present in the ring being formed, cyclization occurs in the 6-*endo* mode.[15] Wilt has carried out the most comprehensive study[15b] with silicon at various positions in the chain (Table 2), and has concluded that the presence of the long Si-C bonds lengthens the chain sufficiently to slow the rate of 5-*exo* closure. The rate of 6-*endo* closure remains essentially unchanged from the parent system (entry 1).

One special case which should be mentioned is the reaction involving vinyl radicals. The ultimate product is often found to be the six membered ring,[16] but the above kinetic factors do not necessarily apply, as the process has been shown to go via a rearrangement (Scheme 2).[16a] The initial closure is 5-*exo*, but under the reaction conditions, radical **26** rearranges to **28** via intermediate radical **27**.

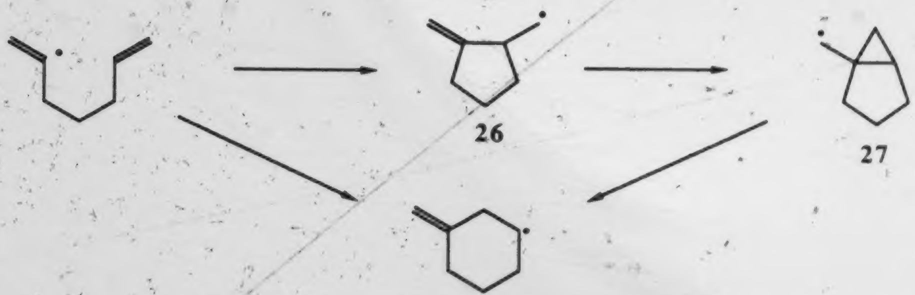
TABLE 2

Relative Rates of Radical Ring Closure (Si in ring) at 25°C

	Starting Radical	Products		k *exo*	k *endo*
1				1	0.02
2				0.03	0.06
3				-[a]	-[b]
4				0.3	0.02

[a] No 5-*exo* product was detected. [b] No kinetic data was provided, but 6-*endo* closure was observed.

SCHEME 2



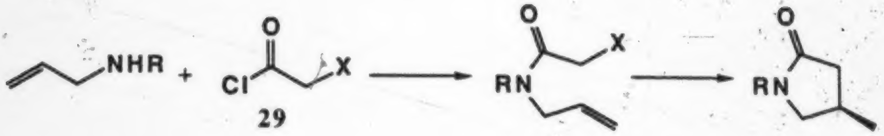
SYNTHETIC APPROACHES TO RADICAL CYCLIZATION

As mentioned earlier, the synthetic utility of radical cyclization is largely dependent on the ease with which one can assemble the precursors for cyclization. In this section, a review of the recent literature is given based on the methodology used to construct compounds that are properly constituted to undergo radical closure.

Use of Amines and Amides

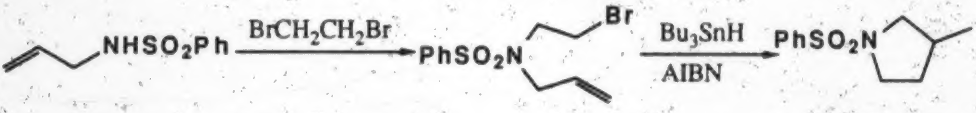
Radical cyclization, when the radical source and the radical trap are linked via a nitrogen atom, is a convenient route towards a wide variety of nitrogen heterocycles.[17,18,19] Simple nitrogen heterocycles, i.e., pyrrolidines and lactams, can be constructed using a variety of techniques[17] of the same general type.* For example, acylation of a protected allyl amine with a substituted acetyl chloride **29** (where X is a homolyzable substituent) results in a amide that contains a radical source and a radical trap. Homolytic cleavage of the C-X bond, followed by radical closure produces a lactam (eq.23).[17a]

*There are more than thirty different groups that have reported the synthesis of simple hydrofurans, pyrrolidines, lactones, and lactams via routes similar to that shown. The examples given are representative of this plethora of activity.


NHR
+
O
Cl
X
29
O
X
RN
O
RN

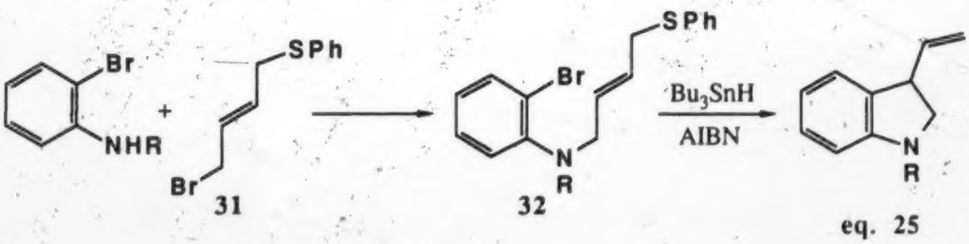
eq. 23

Pyrrolidines are likewise obtained from radical cyclization of **30**, which is derived by *N*-alkylation with dibromoethane (eq 24).[17b]


NHSO2Ph
BrCH2CH2Br
PhSO2N
Br
Bu3SnH
AIBN
PhSO2N

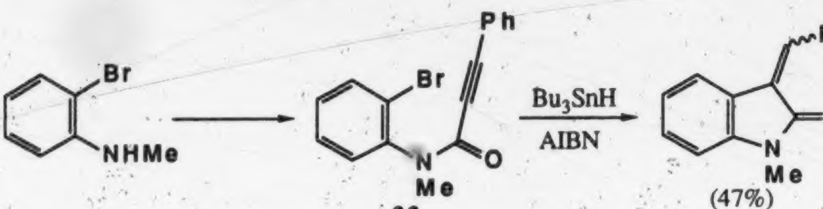
eq. 24

Polycyclic compounds are also readily available by this basic approach. Indole alkaloids can generally be constructed in two steps from *ortho*-haloanilines.[19] Ueno[19a] achieves this via *N*-alkylation with allylic bromide **31**, followed by radical cyclization of **32** (eq. 25).


Br
NHR
+
SPh
Br
31
Br
N
R
32
SPh
Bu3SnH
AIBN
N
R

eq. 25

Bowman[19b] made use of an amide linkage in a comparable example (see **33**, eq. 26).



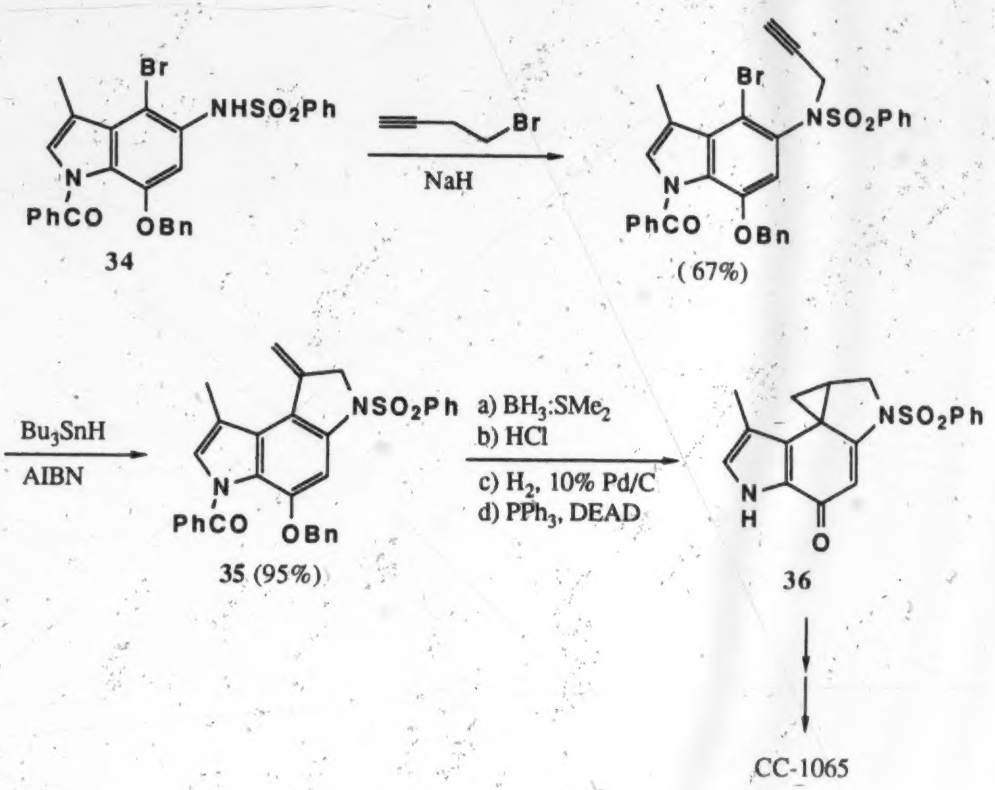
33

eq. 26

Boger used a propargyl group as a radical acceptor, in a key step in the synthesis of the CPI portion (**36**, Scheme 3) of the potent antibiotic, CC-1065.[19c] Treatment of *ortho*-bromosulfonamide **34** with propargyl bromide followed by radical closure, installed the 5-membered heterocycle (see **35**) in 63% yield over two steps. The *exo* methylene group then served in formation of the cyclopropane unit in **36** that was required for the total synthesis of the natural product.

Pyrrolizidine alkaloids have also been synthesized using this type of technology.[20] Hart[8b] devised a route based on the Mitsunobu coupling of various 3-butenols to succinimide (see **37**, Scheme 4). Conversion of one of the carbonyls to a sulfide gives compound **38** which is suitably constituted for cyclization.

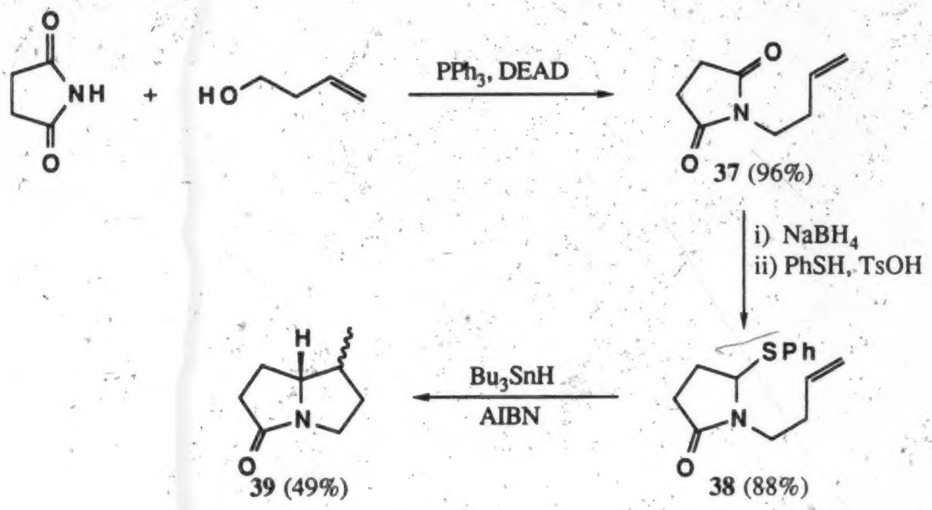
SCHEME 3



Br
NHSO₂Ph
N
PhCO
OBn
34
Br
NaH
Br
NSO₂Ph
N
PhCO
OBn
(67%)
Bu₃SnH
AIBN
NSO₂Ph
N
PhCO
OBn
35 (95%)
a) BH₃:SMe₂
b) HCl
c) H₂, 10% Pd/C
d) PPh₃, DEAD
NSO₂Ph
N
H
O
36
CC-1065

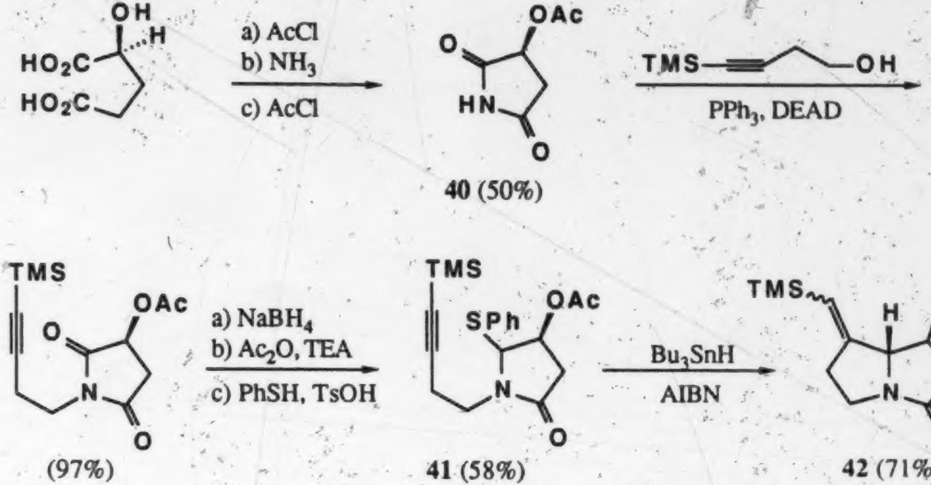
In this particular example, the pyrrolizidine system **39** was only produced in 49% yield due to competition with *endo* closure. However, by use of a protected acetylene unit (see Scheme 5), Hart constructed a compound that led cleanly to a functionalized pyrrolizidine system.[20a] Imide **40** was available in three steps from malic acid. Coupling with 4-(trimethylsilyl)-3-butyne-1-ol as before, and conversion of the carbonyl to a sulfide gave the cyclization precursor **41** in 56% overall yield. Radical closure produced pyrrolizidine **42** which served as an advanced intermediate towards the synthesis of several alkaloids of this class (see compounds **43-45**).

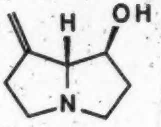
SCHEME 4


O
NH
O
+
HO
PPh$_3$, DEAD
O
N
O
37 (96%)
i) NaBH$_4$
ii) PhSH, TsOH
SPh
N
O
38 (88%)
Bu$_3$SnH
AIBN
H
N
O
39 (49%)

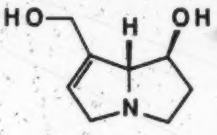
Subsequently, other groups have reported the synthesis of other pyrrolizidine alkaloids, employing this Mitsunobu coupling-radical closure technology.[21]

SCHEME 5

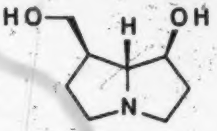

OH
H
HO2C
HO2C
a) AcCl
b) NH3
c) AcCl
OAc
O
HN
O
40 (50%)
TMS
OH
PPh3, DEAD
TMS
OAc
O
N
O
(97%)
a) NaBH4
b) Ac2O, TEA
c) PhSH, TsOH
TMS
SPh
OAc
N
O
41 (58%)
Bu3SnH
AIBN
TMS
H
OAc
N
O
42 (71%)



43

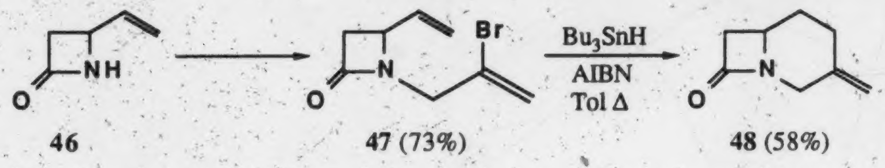


44

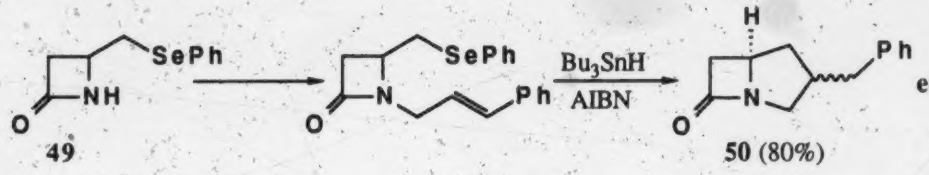


45

Radical cyclization involving amide chemistry has also found extensive application in the synthesis of bicyclic β-lactams.^{8a,22} *N*-Alkylation of readily available 4-substituted azetinones, represents an efficient route to both carbacephams and carbapenams. Parsons' method^{22a} involves the treatment of vinyl substituted **46** with 2,3-dibromopropene, to afford a vinyl bromide **47** (eq. 27). Radical cyclization using a stannane in refluxing toluene produced the expected carbacepham **48** in moderate yield. Alternatively, the radical trap may be attached to the nitrogen. Bachi[8a] *N*-alkylated the azetidinone **49**, which contains a selenide as the radical source, with cinnamyl bromide. Radical closure in a 5-*exo* manner, gave a good yield of the carbapenam **50** (eq. 28).


O
NH
46
Br
O
N
47 (73%)
Bu_3SnH
AIBN
Tol Δ
O
N
48 (58%)

eq. 27

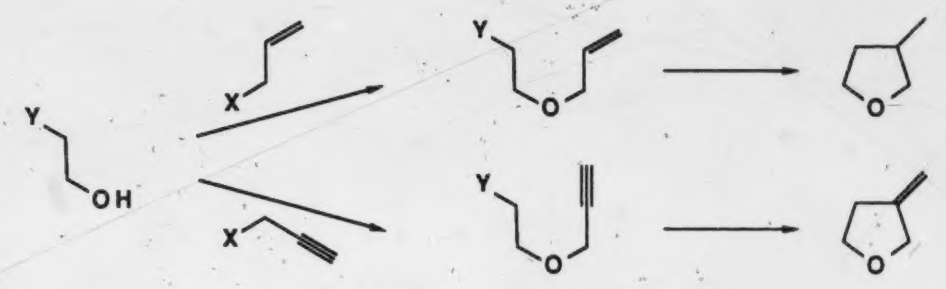

SePh
O
NH
49
SePh
O
N
Ph
Bu_3SnH
AIBN
H
Ph
O
N
50 (80%)

eq. 28

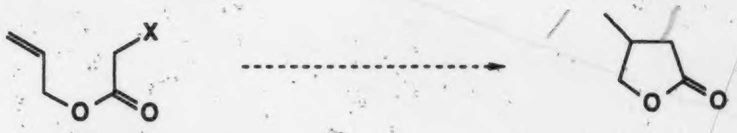
Use of Ethers and Esters

This methodology is similar to that of amines and amides, and lends itself to the synthesis of hydrofurans[23] and lactones.[24] Hydrofurans are most commonly derived via ether linkage of a 2-haloethanol unit, and either allyl or propargyl halides according to Scheme 6.[23a]

SCHEME 6



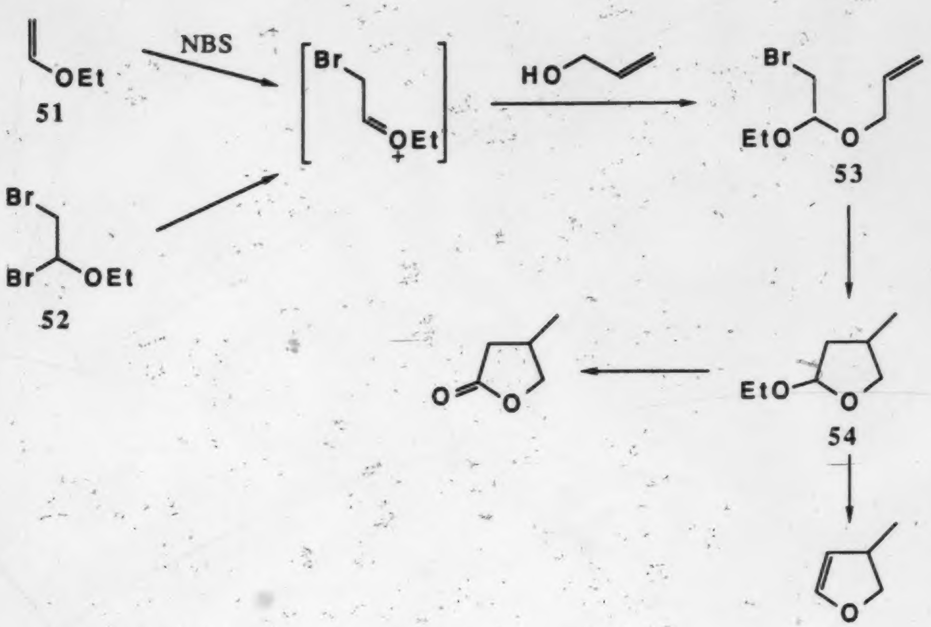
The formation of lactones via eq. 29 is not a viable process.[13] Therefore, an alternative route was developed by Stork (Scheme 7).[24a]



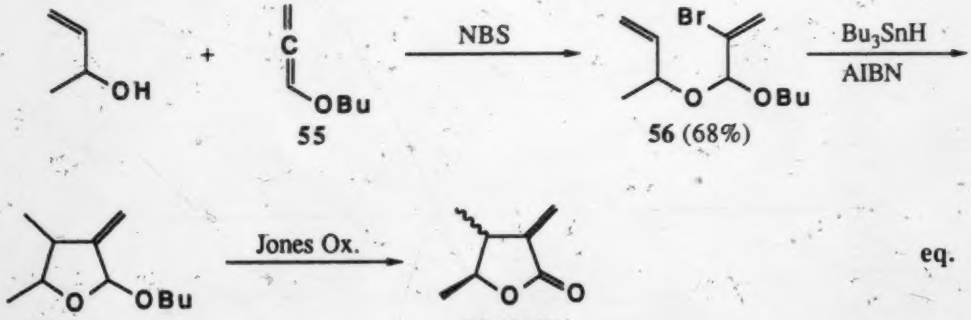
eq. 29

Formation of a mixed acetal from an allylic alcohol, using either vinyl ether **51** or dibromoethyl ether **52**, leads to the cyclization precursor **53**. Radical closure produces acetal **54**, which, after oxidation, completes a convenient route to a lactone. Alternatively, an elimination reaction produces a dihydrofuran.[24b]

SCHEME 7


NBS
OEt
51
Br
Br
OEt
52
Br
OEt
HO
Br
EtO
O
53
O
O
EtO
O
54
O

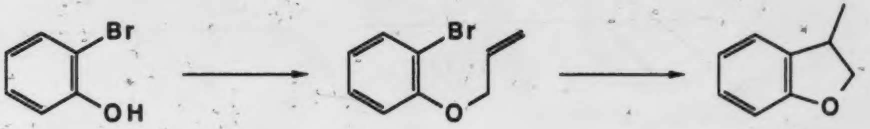
Ueno conducted a similar series of reactions towards the synthesis of α-methylene butyrolactones using an alkoxy allene (eq. 30).[24c]


OH
+
C
OBu
55
NBS
Br
O
OBu
56 (68%)
Bu_3SnH
AIBN
O
OBu
(62%)
Jones Ox.
O
O
57 (64%)

eq. 30

Treatment of the allenyl ether **55** with NBS and an allylic alcohol gave vinyl bromide **56** in good yield. Radical cyclization followed by Jones oxidation produced the desired lactone **57**.

In a comparable approach to the synthesis of indoles, benzofurans and benzopyrans are readily constructed from *ortho*-halo phenols.[25] Treatment with an allyl halide followed by radical closure in a 5-*exo* manner leads to the expected benzofuran **58** (eq. 30).[25a] Benzopyrans are constructed using similar chemistry, via a 6-*exo* radical cyclization.[25b]

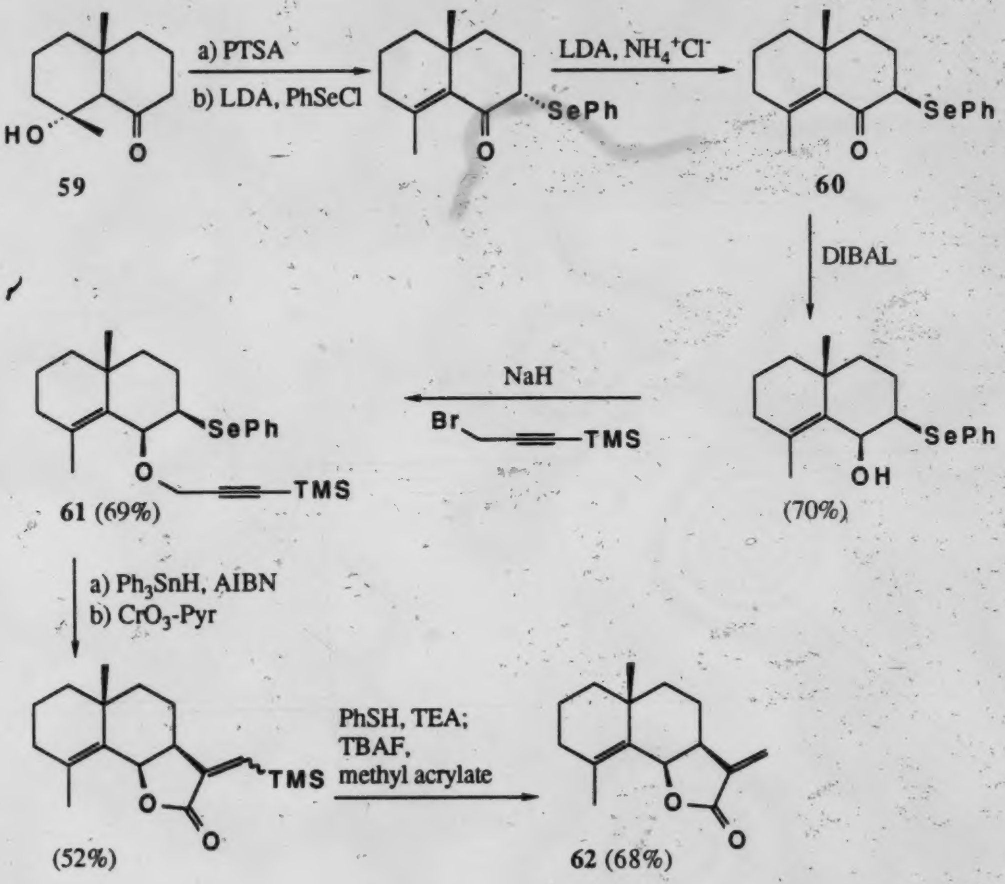


58

eq. 31

The methodologies mentioned here are all quite simple, and therefore have wide applicability. For example, Clive and Joussef[26] have recently used a radical cyclization involving a propargyl ether, which after oxidation, gave the lactone portion of frullanolide **62** (Scheme 8). Ketone **59** is a known compound, that was converted into α-(phenylseleno) ketone **60**, an advanced intermediate that contained the radical source. Reduction to the alcohol, followed by *O*-alkylation with the protected propargyl bromide, provided the cyclization precursor **61** in good overall yield. Triphenyltin hydride promoted radical closure, then oxidation and deprotection produced the natural product **62**.

SCHEME 8


a) PTSA
b) LDA, PhSeCl
SePh
LDA, $NH_4^+Cl^-$
SePh
DIBAL
NaH
Br
TMS
SePh
OH
SePh
O
TMS
a) Ph_3SnH, AIBN
b) CrO_3-Pyr
TMS
PhSH, TEA;
TBAF,
methyl acrylate
HO
O
O
O
O
O
O
O

59

60

(70%)

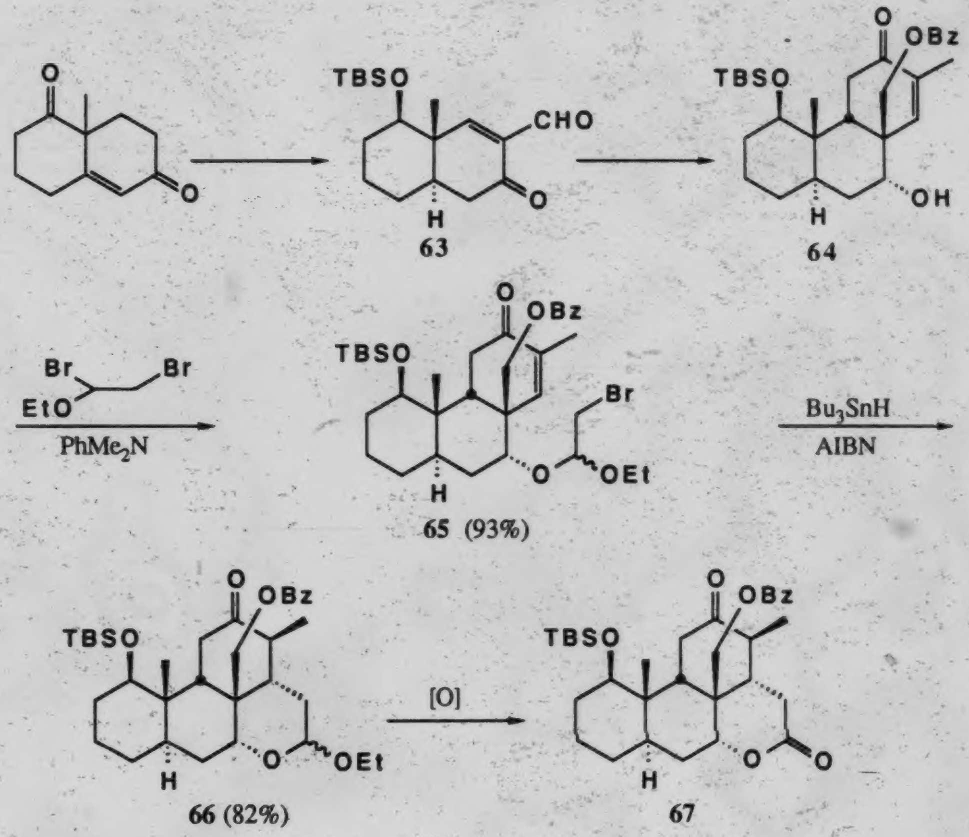
61 (69%)

(52%)

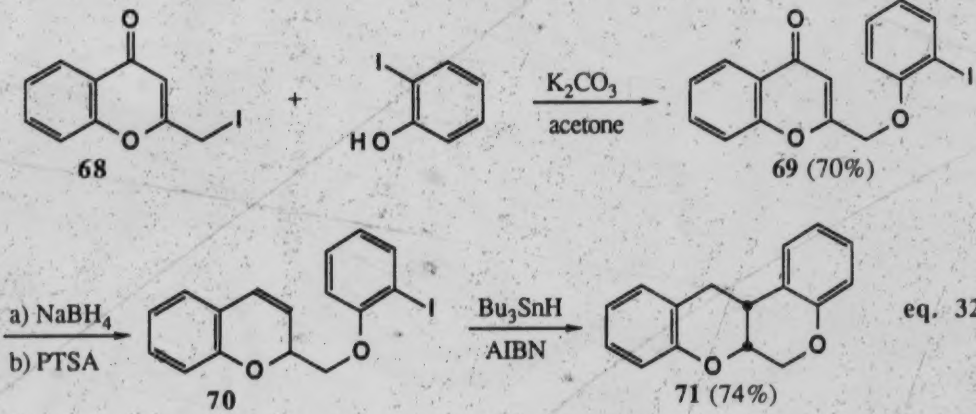
62 (68%)

The lactone portion of quassinoid **67** was installed via the mixed acetal methodology (Scheme 9).^{27} The tricyclic alcohol **64** containing the enone system as the radical trap, was derived via Diels-Alder reaction of enone **63**. Treatment of **64** with dibromoethyl ethyl ether gave the mixed bromo acetal **65**, that underwent cyclization to give lactol **66** in excellent overall yield.

SCHEME 9


TBSO
CHO
H
63
OBz
OH
64
Br
Br
EtO
PhMe2N
Br
OEt
65 (93%)
Bu3SnH
AIBN
66 (82%)
[O]
67

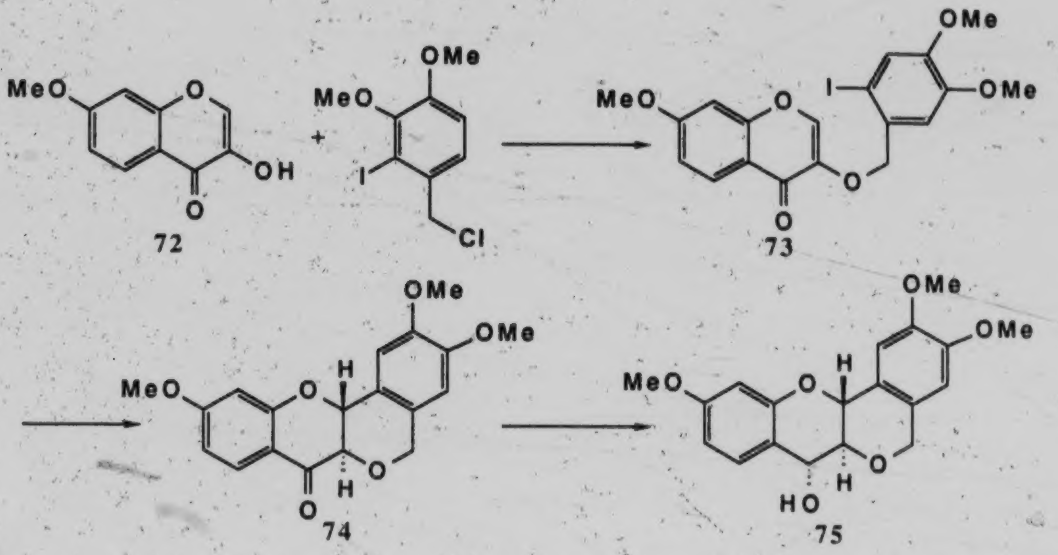
Whiting based his synthesis of a benzopyran substructure, present in the rotenoid skeleton **71**, on ether formation followed by a 6-*exo* closure (eq. 32).[28a] Iodide **68** was treated with *ortho*-iodophenol to give ether **69**. Reduction of the enone system, followed by elimination, moved the double bond to the desired position for the cyclization process (see **70**). Treatment with tributyltin hydride produced the rotenoid skeleton **71**.



eq. 32

A similar approach has recently been reported for the total synthesis of a derivative of a natural product **75** (Scheme 10).[28b] Chromanol **72** was treated with *ortho*-iodobenzyl chloride affording benzyl ether **73**. In this case, formation of the aryl radical resulted in a 6-*endo* Michael closure to give **74**, which represents the carbon framework of the biologically active natural product, peltogynol **75**.

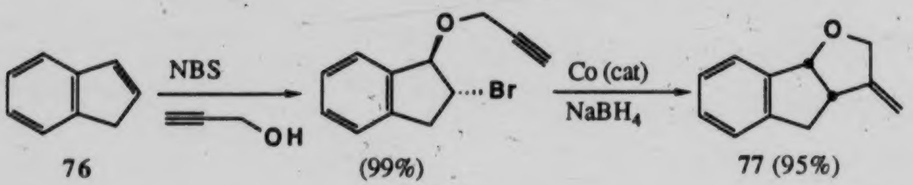
SCHEME 10



Use of Olefins

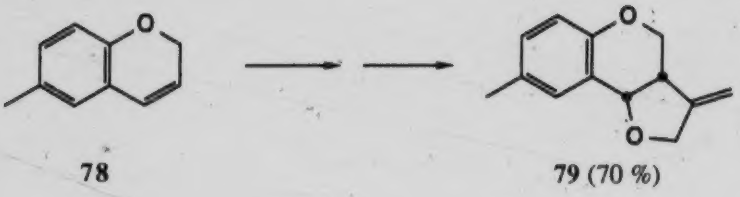
Addition of two units across a double bond is a technique that lends itself to convenient assembly of precursors for radical cyclization. Many variations of this idea have appeared in the literature and the method is clearly useful in the synthesis of polycyclic compounds.

Bromoether formation from an olefin using NBS and propargyl or allyl alcohols is an efficient route to oxygen heterocycles.[29] In this way, indene was transformed into a hydrofuran derivative **77** in excellent yield (eq. 33).[29a]


NBS
OH
O
Br
Co (cat)
NaBH4
O
76
(99%)
77 (95%)

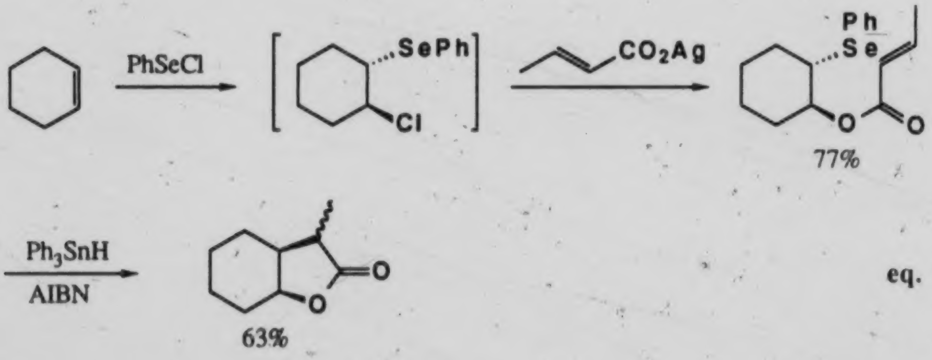
eq. 33

This same sequence of reactions has been used in the partial synthesis of the pterocarpan skeleton **79** from benzopyran **78** (eq. 34).[29b]



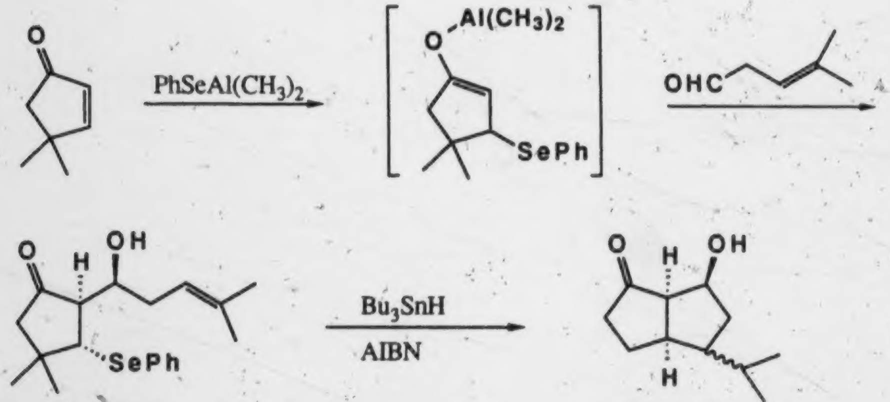
eq. 34

Bicyclic lactones have been synthesized via addition of phenylselenyl chloride across a double bond (eq. 35).[11a] The chloride was then displaced by crotonate, and 5-*exo* cyclization provided an efficient route to the lactone.


PhSeCl
SePh
Cl
CO2Ag
Ph
Se
O
O
77%
Ph3SnH
AIBN
O
O
63%

eq. 35

In terms of assembling compounds for radical cyclization from carbon-carbon double bonds, the use of Michael acceptors is well documented.[30-33] The following are three contrasting examples involving the synthesis of both *cis*- or *trans*-bicyclic carbocycles. Livinghouse synthesized a variety of bicyclic carbocycles from cyclic enones.[30a] Michael addition of selenide, and trapping of the resulting enolate with a β,δ-unsaturated aldehyde effected the addition of the radical source and the radical trap in one step (see **80**, eq. 36). Homolysis of the C-Se bond followed by cyclization provided an elegant route to a *cis*-fused bicyclic ketone alcohol **81**.

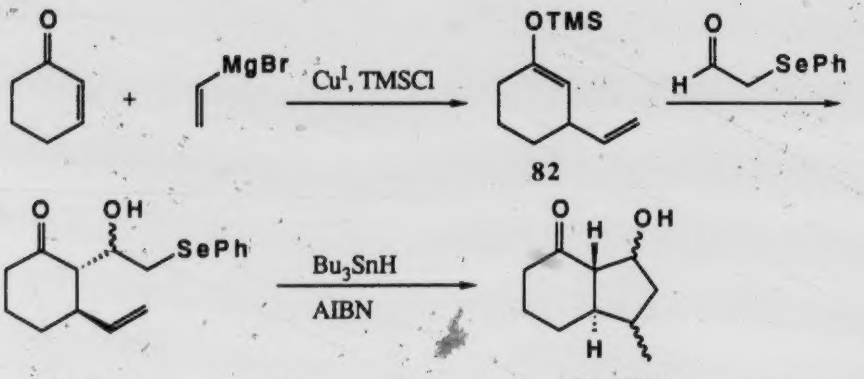


80 (72%)

81 (95%)

eq. 36

In related methods, Michael addition of a vinyl group to cyclohexenone results in an enolate **82** that can be quenched, in an aldol fashion, with (phenylseleno)acetaldehyde, to give the *trans*-substituted cyclohexanone **83** (eq. 37). Radical cyclization then produces the *trans*-fused 6-5 system **84**.[30b]


MgBr
Cu^I, TMSCl
OTMS
SePh
Bu$_3$SnH
AIBN
OH
H

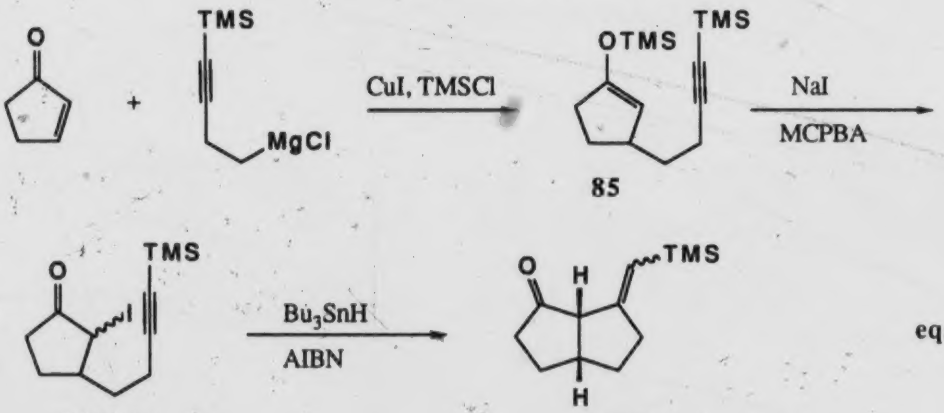
82

83 (56%)

84 (58%)

eq. 37

In a similar example, a homopropargyl group was added in a 1-4 fashion, the resulting enolate **85** was trapped by trimethylsilylchloride (eq. 38). Subsequent treatment with sodium iodide in the presence of a peracid installed the radical source in **86**. In this case, radical cyclization produced the *cis*-fused bicyclic ketone **87**.[30c]


TMS
MgCl
CuI, TMSCl
OTMS
NaI
MCPBA
I
Bu$_3$SnH
AIBN
H

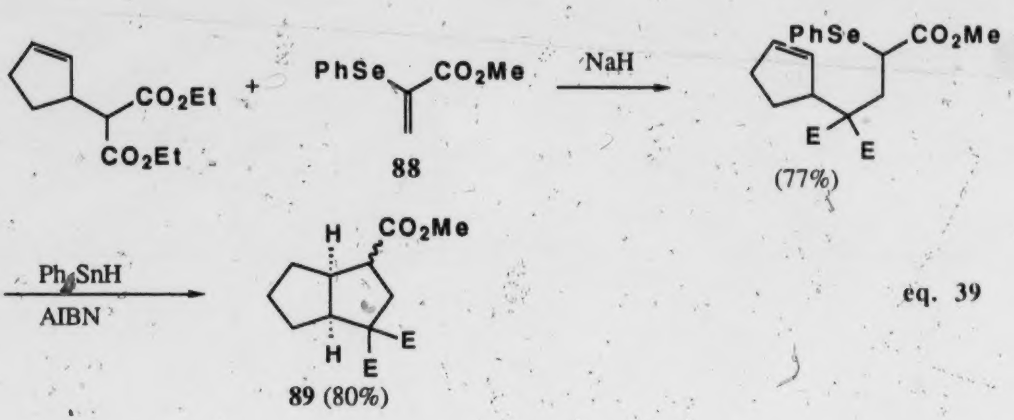
85

86 (61%)

87 (81%)

eq. 38

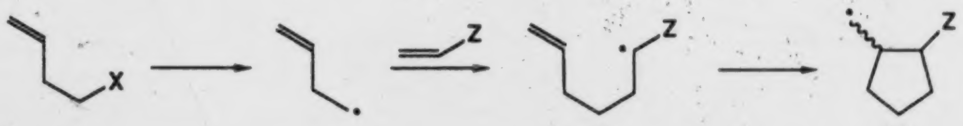
The Michael acceptor may contain the radical source,[31] as in compound **88**, in which case, an anionic Michael addition by an unsaturated unit, followed by radical closure produces the *cis*-fused bicyclic compound **89** in good overall yield (eq. 39).


CO2Et
CO2Et
+
PhSe
CO2Me
88
NaH
PhSe
CO2Me
E
E
(77%)
Ph3SnH
AIBN
H
CO2Me
H
E
E
89 (80%)

eq. 39

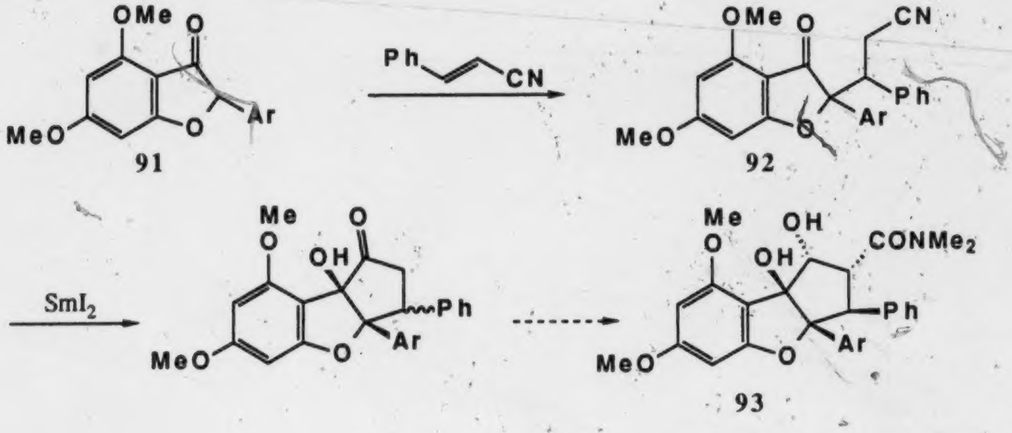
A variation of this technique involves radical addition to a Michael acceptor followed by cyclization in one step, according to Scheme 11.[32] However, yields can be low due to the subsequent reaction of radical **90** with the excess of Michael acceptor.

SCHEME 11



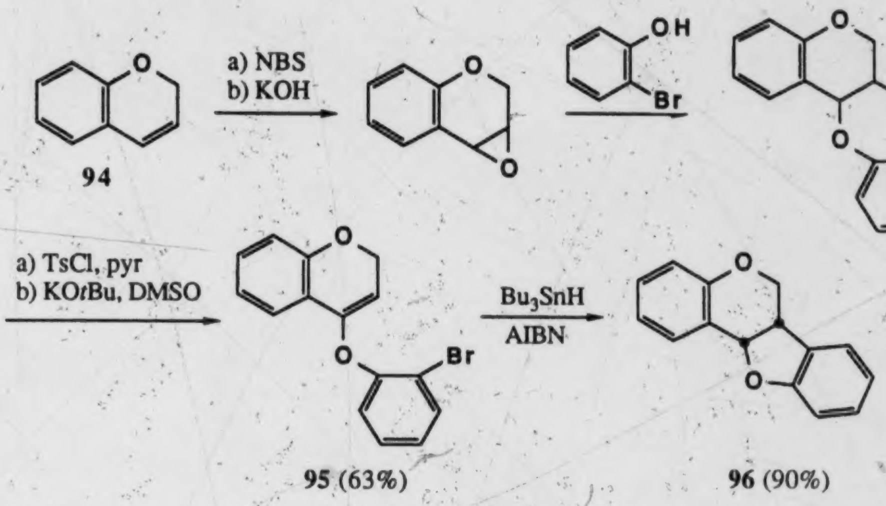
90

A similar approach has been applied to a total synthesis of the anticancer agent rocaglamide **93**.[33] The Michael reaction involves the addition of ketone **91** to 3-phenylacrylonitrile. The cyclization is initiated by samarium diiodide. The ketone unit in **92** acts as the radical source and the nitrile is the radical trap. This methodology provided the carbon framework required to complete the synthesis of rocaglamide **93** (eq. 40).


OMe
O
MeO
O
Ar
91
Ph
CN
OMe
O
CN
Ph
Ar
MeO
O
92
SmI2
Me
O
OH
O
Ph
MeO
O
Ar
Me
O
OH
OH
CONMe2
Ph
MeO
O
Ar
93

eq. 40

Other researchers have converted olefins into precursors for radical closure via the corresponding epoxide and subsequent ring opening.[34] This procedure has been used to make both lactones and furans, and was involved in a key step in the synthesis of the pterocarpan skeleton (eq. 41).[34a] Epoxidation of benzopyran **94**, followed by epoxide ring opening with *ortho*-bromophenol provided the radical source; tosylation and elimination produced the radical trap. The enol ether **95** was assigned the structure shown, but in the cyclization step, the double bond must have moved to accommodate a 5-*exo* closure to produce the pterocarpan **96**, which was formed in excellent yield.

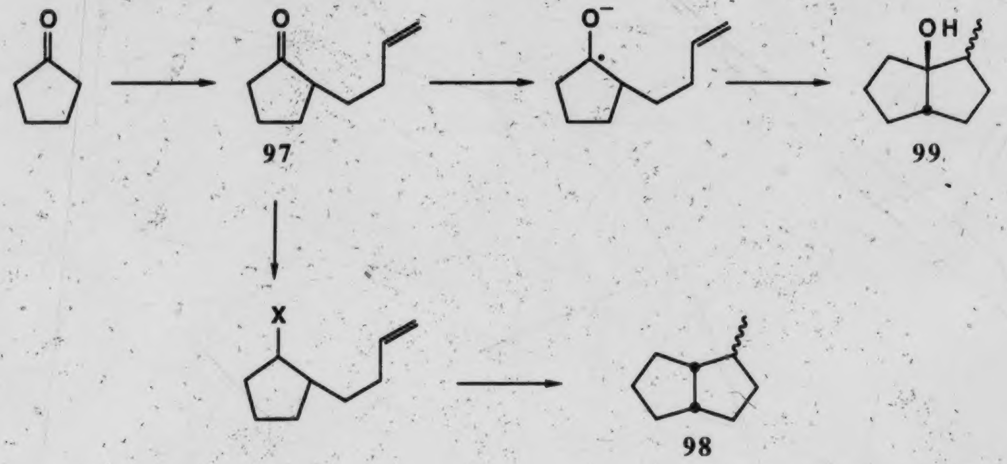


eq. 41

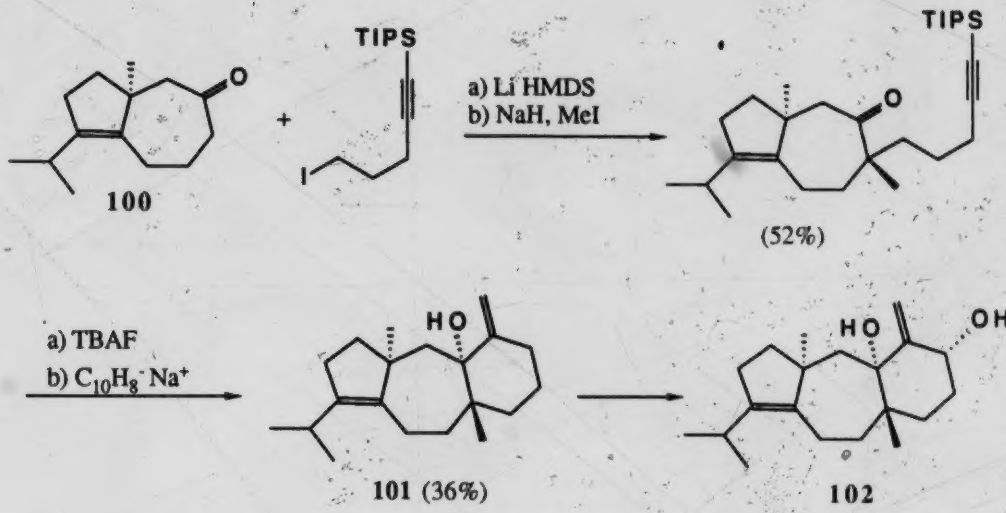
Use of Carbon Alkylation

Alkylation on carbon (usually *alpha* to a carbonyl) by a homoallyl or homopropargyl moiety, followed by radical cyclization is a simple but convenient route to carbocycles (Scheme 12).[35-37] Conversion of the ketone in **97** to a homolyzable unit allows for formation of the bicyclic compound **98**.[35] Alternatively, the ketone may be the radical source directly, by exposure to samarium diiodide, by electrolysis, or by photochemical methods, in which cases the product **99** contains an angular hydroxyl group.[36]

SCHEME 12

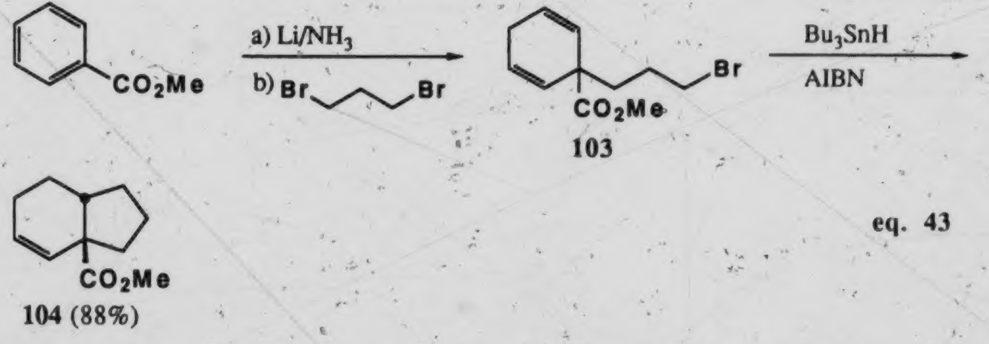


This procedure has been used in the total synthesis of a marine natural product of the dolastane diterpene class (see **102**, eq. 42).[36a] Alkylation of bicyclic ketone **100** with a protected acetylide, followed by deprotection and sodium naphthylide-induced radical closure, produced **101**, which has the carbon skeleton required for the natural product.


TIPS
a) Li HMDS
b) NaH, MeI
TIPS
100
(52%)
a) TBAF
b) $C_{10}H_8^- Na^+$
HO
HO
OH
101 (36%)
102

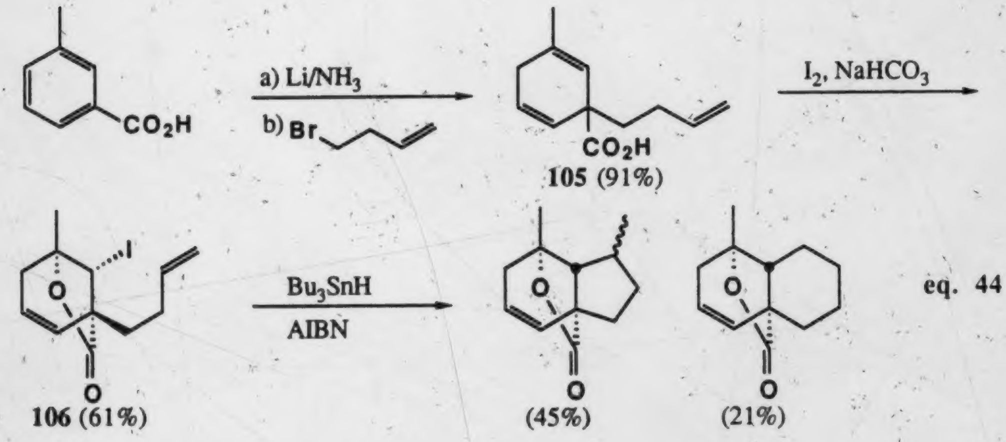
eq. 42

Beckwith demonstrated a route that produces bicyclic compounds from benzoic acid (eq. 43).[38a] Birch reduction of the acid, and trapping of the resulting anion with 1,3-dibromopropane, quickly affords compound **103**, which is suitably constituted for radical closure. Treatment of **103** with tributyltin hydride gave an excellent yield of the *cis*-fused 6-5 system **104**.


CO_2Me
a) Li/NH_3
b) Br Br
Br
CO_2Me
103
Bu_3SnH
AIBN
CO_2Me
104 (88%)

eq. 43

In a variation of this procedure, Hart alkylated the Birch reduction product with an olefin (see **105**, eq. 44).[8c] An iodolactonization installed the radical source, and at the same time, determined the ring fusion geometry for the cyclization step. Homolysis of the C-I bond in **106** resulted in a radical closure. However, in this system, good *exo-endo* selectivity was not obtained. This problem was easily overcome by the use of a protected aldehyde (see **107**, eq. 45) followed by its conversion (via Horner-Emmons chemistry) to olefin **108**.[38b]



105 (91%)

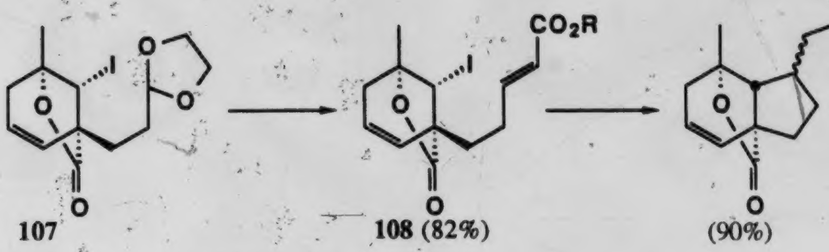
106 (61%)

(45%)

(21%)

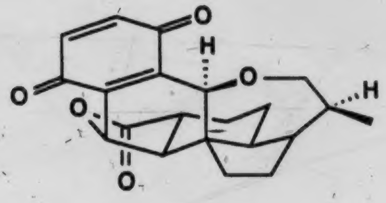
eq. 44

In this case, cyclization went cleanly in a 5-*exo* manner (eq. 45). Hart used this methodology in the synthesis of the *trans*-ring fused 6-5 system of several natural products including pleurotin **109**, an antitumour antibiotic.[38b]



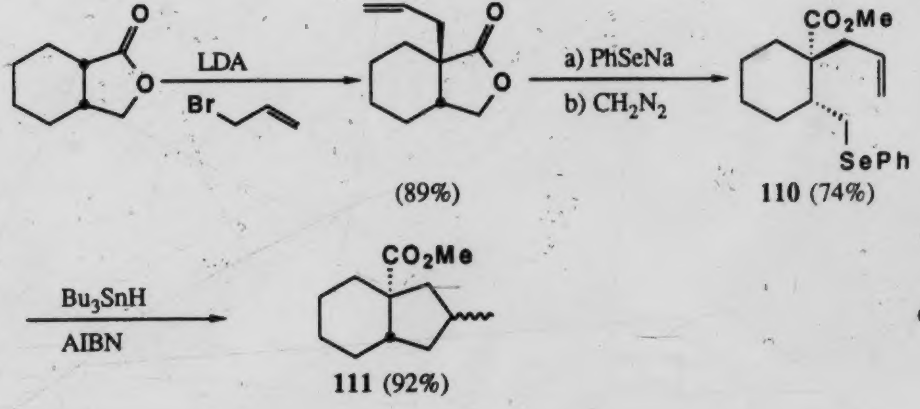
107 108 (82%) (90%)

eq. 45



109

Alkylation of *cis*-fused bicyclic lactones with allyl bromide, followed by selenide promoted ring opening constitutes an additional route to bicyclic compounds.[39] The lactone controls the geometry of the alkylation, such that after ring-opening, the selenide and the olefin bear a *trans* relationship to each other (see **110**, eq. 46). Radical cyclization then produces the *trans*-fused system **111**.


LDA
Br
a) PhSeNa
b) CH2N2
CO2Me
SePh
Bu3SnH
AIBN
CO2Me

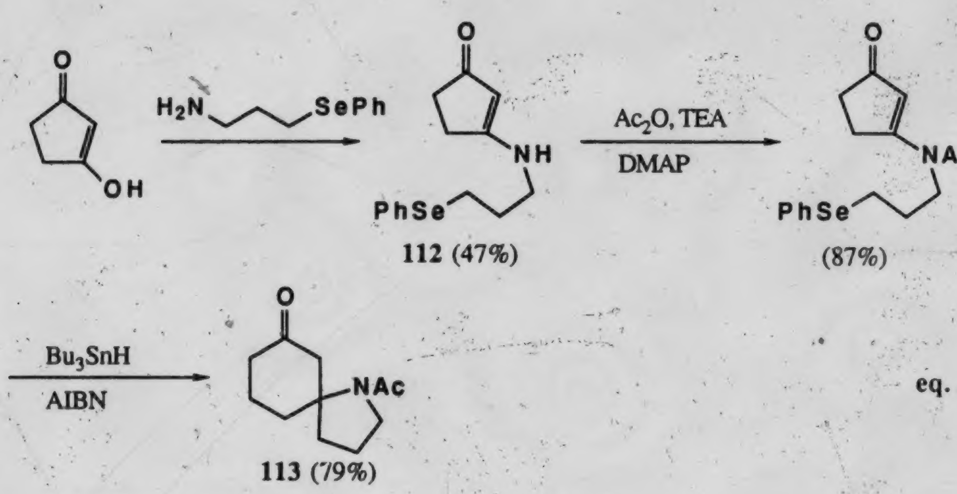
(89%) 110 (74%)

111 (92%)

eq. 46

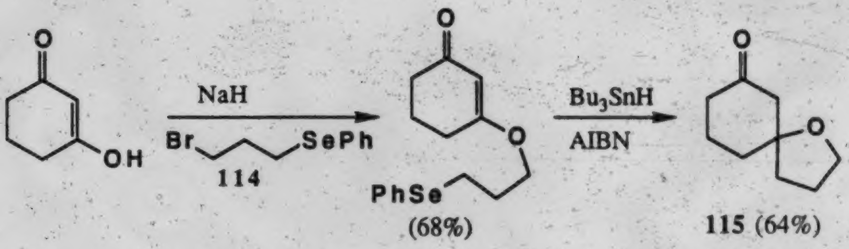
Use of Carbonyl Group

Reactions that take place directly on the carbonyl provide further routes to precursors for radical closure. This has proven to be a convenient approach to spiro compounds. Simpkins devised a route to both spiro amides and spiro ethers.



eq. 47

Condensation of a 1,3-diketone with an amine which contains the radical source, produces the enamine **112**, which, after acylation, can close to form the protected spiro amine **113** (eq. 47).[40a] The corresponding spiro ether **115** is obtained via *O*-alkylation with bromo selenide **114** followed by radical cyclization (eq. 48).[40b]

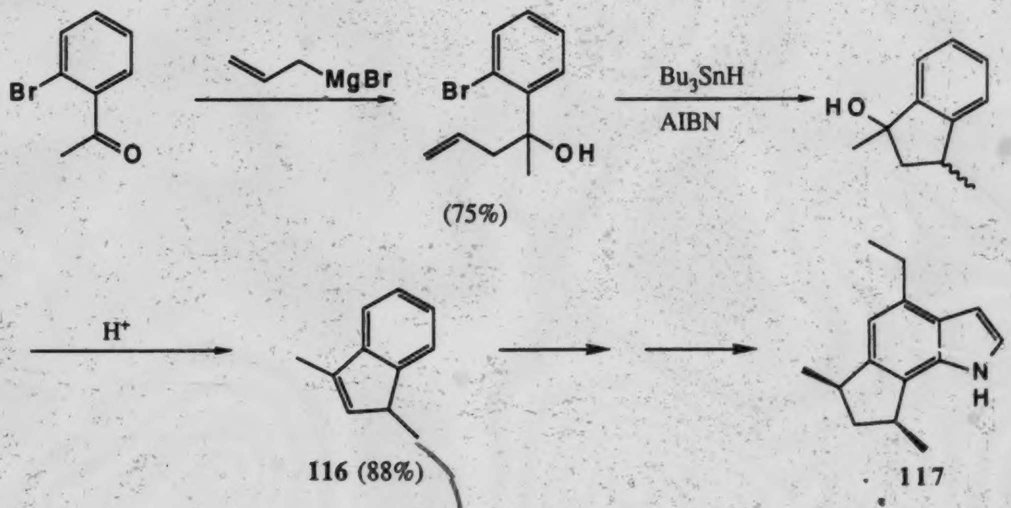

NaH
Br
SePh
114
PhSe
(68%)
Bu₃SnH
AIBN
(64%)

115 (64%)

eq. 48

Carbonyls have also been the starting point in radical cyclization procedures that involve use of the Grignard reaction. The addition of an allyl unit to *ortho*-bromoacetophenone produced the cyclization precursor, as shown in Scheme 13. Radical cyclization followed by an elimination gave the indane **116**, which was used for the total synthesis of trikentrin A **117**, a biologically active marine natural product.[41]

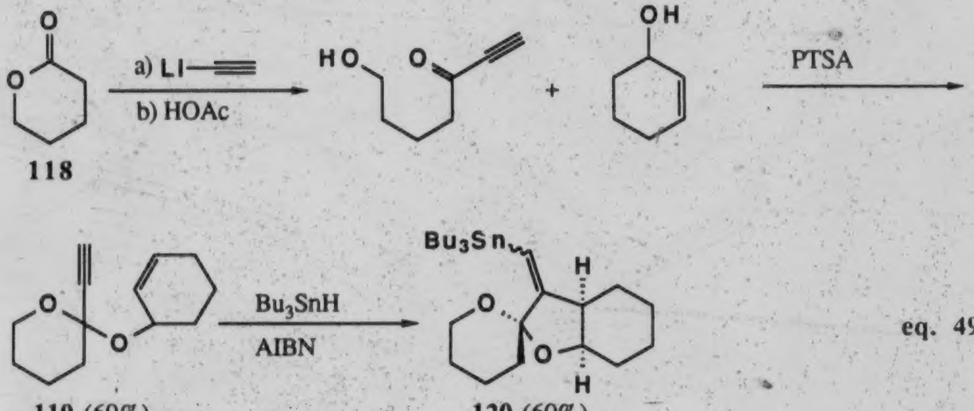
SCHEME 13


Br
MgBr
Br
OH
(75%)
Bu₃SnH
AIBN
HO
H⁺
N
H

116 (88%)

117

Parsons has reported a radical cyclization route to spiro acetals in his model studies towards the synthesis phyllanthocin **121** (eq. 49).[42] Addition of acetylide to lactone, **118**, followed by mixed acetal formation involving an allylic alcohol, produces the cyclization precursor **119**. Treatment with stannane, generates a vinyl radical that closes onto the olefin to give the desired spiro acetal **120**.

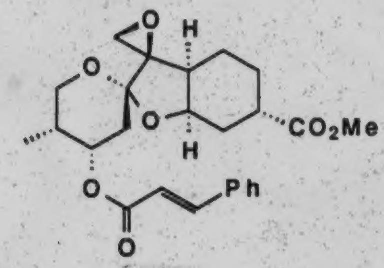

a) Li—≡
b) HOAc
HO
O
+
OH
PTSA
O
O
Bu$_3$SnH
AIBN
Bu$_3$Sn
H
O
O
H

118

119 (69%)

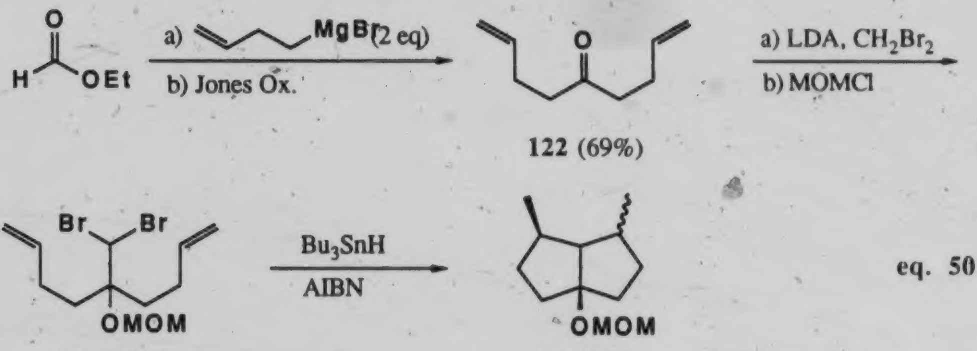
120 (60%)

eq. 49


O
H
O
O
H
CO$_2$Me
O
Ph
O

121

Wilcox also used the Grignard reaction to synthesize precursors for a double radical cyclization reaction (eq. 50).[43] Double 4-butenyl addition to ethyl formate, followed by oxidation, afforded the symmetrical ketone **122**. Treatment of **122** with the anion of dibromomethane gave **123**, the dibromide precursor to double cyclization. The addition of tributyltin hydride resulted in two sequential 5-*exo* ring closures, to produce the *cis*-fused 5-5 system **124**.



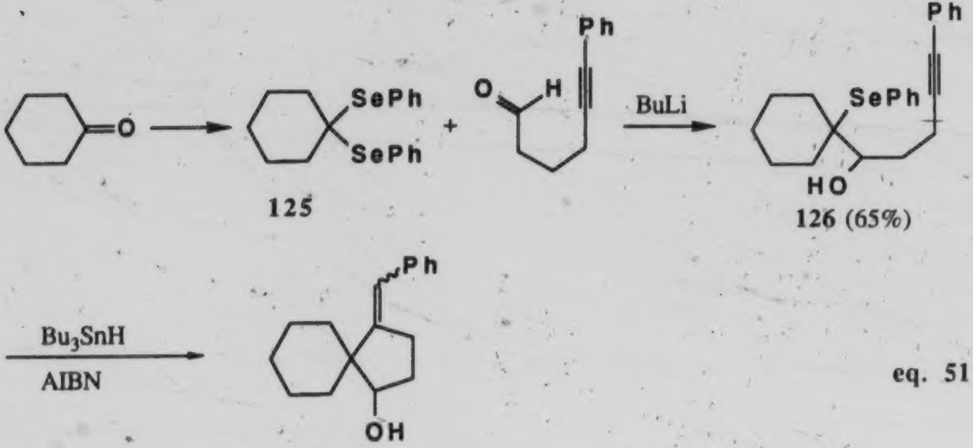
122 (69%)

123 (63%)

124 (45%)

eq. 50

Clive has also developed routes to spiro compounds from ketones via formation of the selenoketal **125** (eq. 51).[44] Treatment with *n*-butyllithium furnished an anion that was trapped with a δ,γ-unsaturated aldehyde to give **126**. Upon radical cyclization, the spiro compound **127** was produced.


SePh
SePh
Ph
BuLi
SePh
HO
Bu$_3$SnH
AIBN
Ph
OH

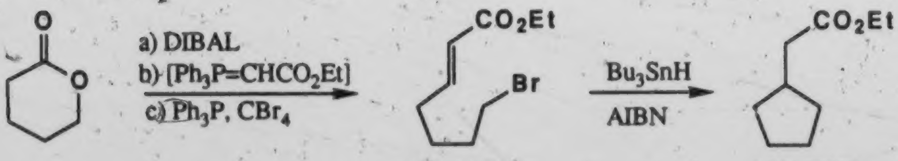
125

126 (65%)

127 (75%)

eq. 51

Use of Wittig chemistry is very important in radical chemistry for the generation of the radical trap from ketones or aldehydes.[45] Hanessian has used this approach in the preparation carbocycles from lactones (eq. 52).[45a] DIBAL reduction of the lactone produces a lactol, i.e., a carbonyl equivalent. Horner-Emmons reaction on the lactol generates the radical trap and also liberates a hydroxyl group which is easily converted to a homolyzable subunit such as bromine, as in **128**. Radical induced cyclization completes the sequence, affording the carbocycle **129**.

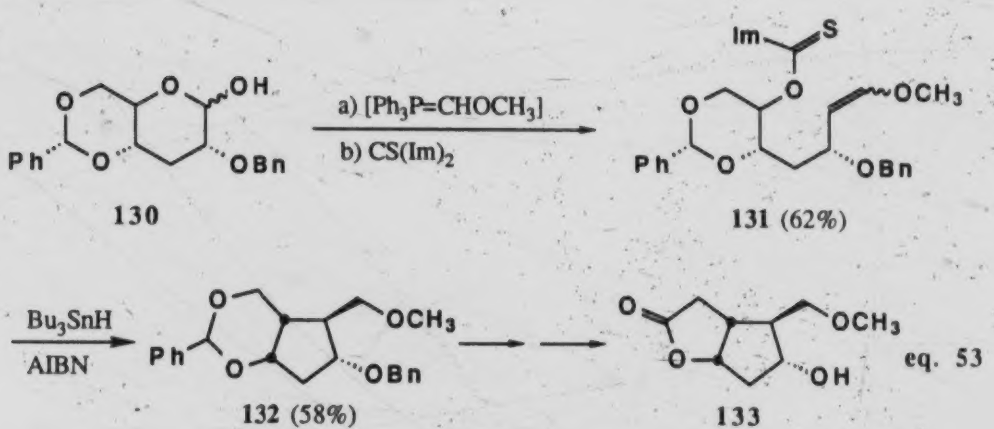

O
O
a) DIBAL
b) [Ph$_3$P=CHCO$_2$Et]
c) Ph$_3$P, CBr$_4$
CO$_2$Et
Br
Bu$_3$SnH
AIBN
CO$_2$Et

128 (68%)

129 (75%)

eq. 52

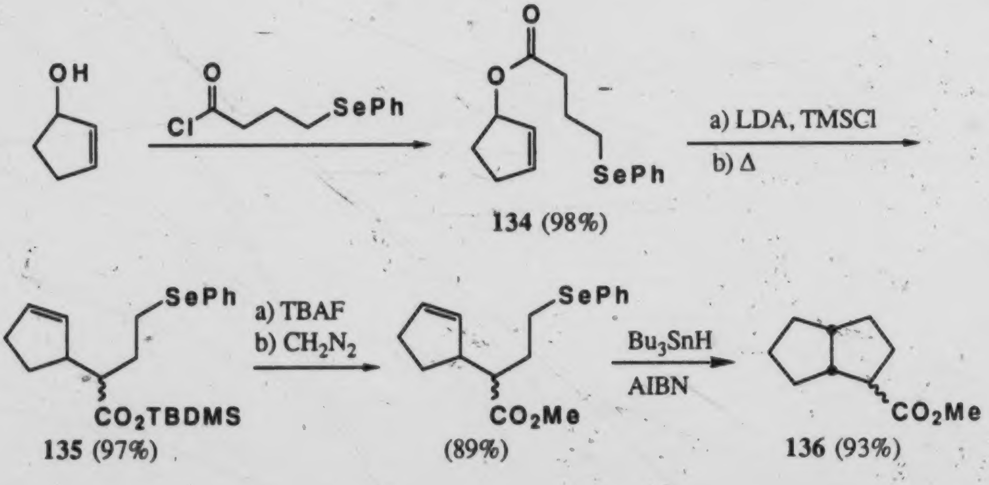
This procedure is extremely useful when applied to sugars derivatives, in that it results in the production of optically active, functionalized carbocycles (see eq. 53).[45b,c]


a) [Ph3P=CHOCH3]
b) CS(Im)2
Bu3SnH
AIBN
130
131 (62%)
132 (58%)
133
eq. 53

The Corey lactone **133** (eq. 53) was synthesized from the carbohydrate derivative **130**, by Wittig reaction, and conversion of the liberated hydroxyl group to its thiocarbonylimidazole derivative **131**.[45b] Radical closure gave the intermediate **132**, which was used to complete the synthesis.

Miscellaneous Routes

There are several other unique routes that use a radical cyclization step in the synthesis of polycyclic systems. One novel technique invokes usage of the Ireland ester enolate rearrangement.[46] This method is initiated by the condensation of an allylic alcohol with an ester containing the radical source (see **134**, eq. 54). Formation of the ester enolate, followed by a thermally induced rearrangement provided **135** which is properly constituted to undergo 5-*exo* cyclization. Conversion to the corresponding methyl ester, followed by treatment with stannane gave *cis*-fused **136**.


OH
O
Cl
SePh
O
O
SePh
a) LDA, TMSCl
b) Δ
SePh
CO₂TBDMS
a) TBAF
b) CH₂N₂
SePh
CO₂Me
Bu₃SnH
AIBN
CO₂Me

134 (98%)

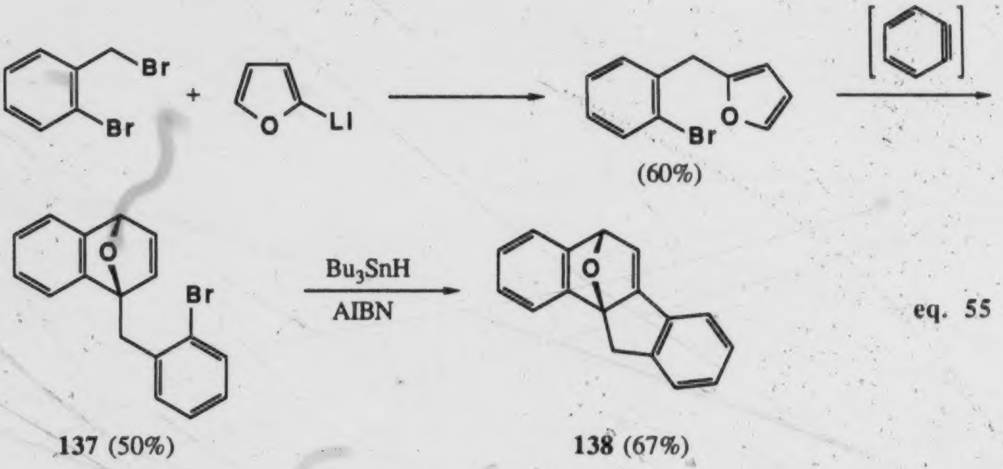
135 (97%)

(89%)

136 (93%)

eq. 54

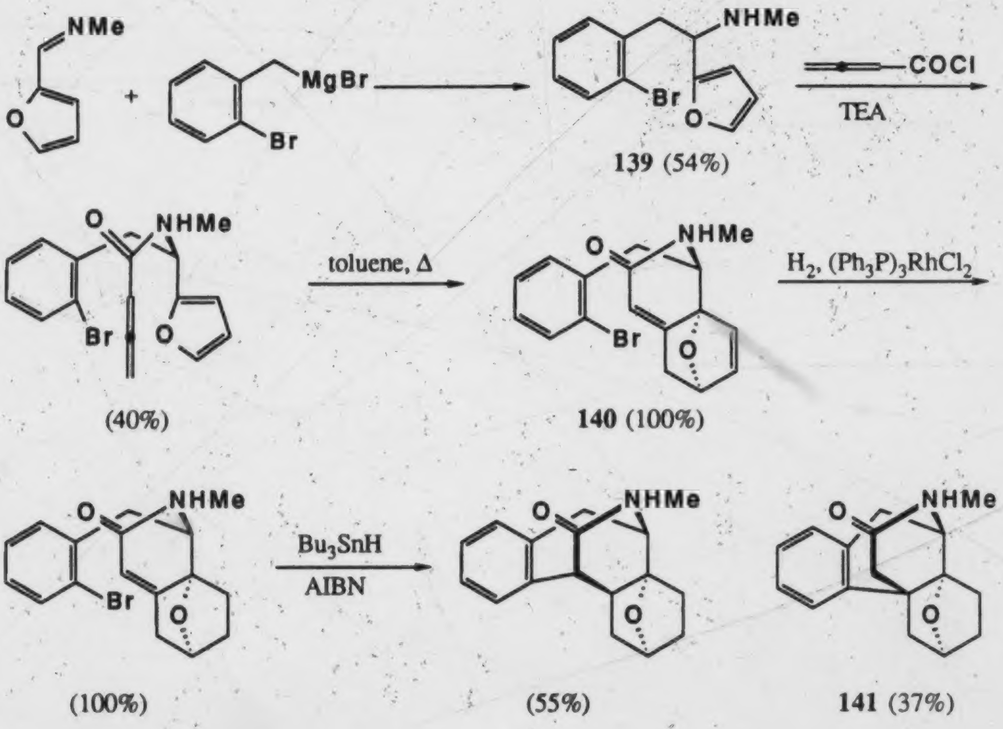
The Diels-Alder reaction is also suitable for use in conjunction with radical cyclization.[47] This methodology requires that either the diene or the dienophile contains a radical source. Hart linked a furan moiety to *ortho*-bromophenol, and then benzyne chemistry promoted cycloaddition to the furan giving **137**. The resulting double bond acts as the radical acceptor and cyclization afforded the polycyclic compound, **138** (eq. 55).[47a]



eq. 55

Harwood designed a synthesis of a morphinan skeleton, based on an intramolecular Diels-Alder reaction (Scheme 14).[47b] Grignard addition to the *N*-methyl imine of furaldehyde, produced amine **139** and acylation with an allenic acid chloride installed the dienophile. Intramolecular cycloaddition provided the desired carbon framework **140**, but in this system there are two potential radical traps. Selective reduction of the undesired olefin, followed by radical closure gave two products, one of which (**141**) represents the desired morphinan skeleton.

SCHEME 14


NMe
O
+
MgBr
Br
NHMe
Br
O
COCl
TEA
139 (54%)
O
NHMe
Br
O
(40%)
toluene, Δ
O
NHMe
Br
O
140 (100%)
H₂, (Ph₃P)₃RhCl₂
O
NHMe
Br
O
(100%)
Bu₃SnH
AIBN
O
NHMe
O
(55%)
O
NHMe
O
141 (37%)

The methods discussed here provide ready access to a wide variety of compounds. Radical cyclization technology has clearly been established as a useful approach for the construction of complex molecules.

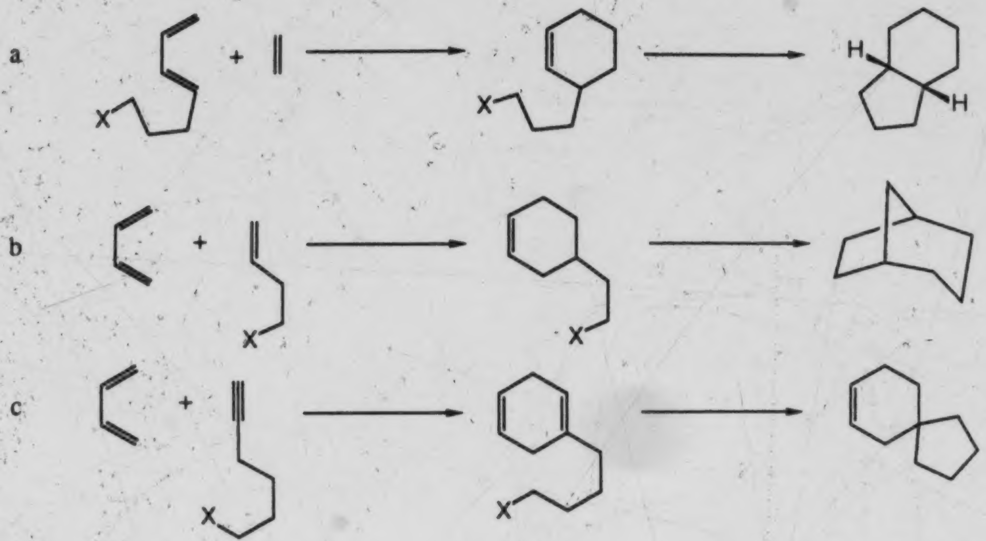
II. RESULTS AND DISCUSSION

The development of radical cyclization technology by the chemical community has taken place over the last fifteen years. However, it has yet to become a widespread technique for the synthesis of complex natural products. The main project described in this thesis is the development of new methodology for rapid assembly of bicyclic compounds. The method consists of two steps of which the first is a Diels-Alder reaction and the second is a radical closure. This sequence provides a concise route to linear, bridged, and spiro bicyclic compounds, including heterocycles. During this work, the effects of electron withdrawing groups on the 6-*endo*/5-*exo* ratio of ring closure were examined.

The Diels-Alder reaction is especially well suited for integration with radical cyclization chemistry because of the inherent formation of a double bond that then acts as a radical trap.[47,48] If either the diene or the dienophile contains a homolyzable substituent, then the potential for a subsequent radical cyclization is introduced.

The initial ideas are summarized in Scheme 15. If the diene was to have a "tail" which contains some group X, such as a halide or selenide, then the product of the Diels-Alder reaction could undergo radical closure in a 5-*exo* manner that would lead to a *cis*-fused[30a] 6-5 system (entry a).

SCHEME 15

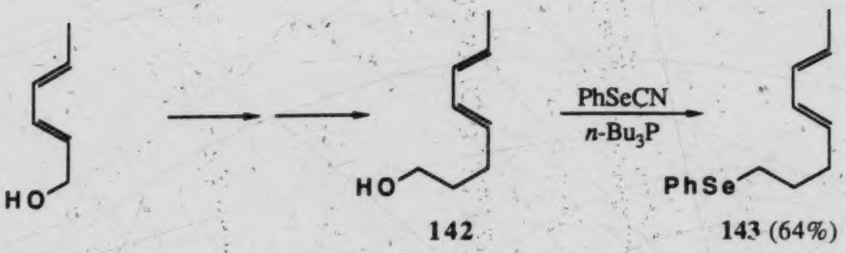


On the other hand, if the dienophile were to contain the radical precursor, then a 5-*exo* closure would lead to a bridged [3.2.1] bicyclic compound (entry b). Thirdly, a Diels-Alder reaction involving an acetylene that contains the radical source could, after 5-*exo* closure, produce a spiro compound (entry c). The work described here is the application and extension of these ideas.

The initial task was the synthesis of the appropriate starting materials containing the homolyzable substituent, X. There are several functionalities to choose from as a radical source. We prefer to generate the radicals from a phenylseleno group.[49] There are a number of reasons for this choice. The phenylseleno group is sufficiently robust to survive a variety of reaction conditions. In several cases (*vide infra*) the synthesis of the starting materials required the use of anionic chemistry. This would be complicated by the presence of a halide,[47] whereas a selenide does not constitute a problem. Oxidations in the presence of a selenide can be problematic but there are several compatible reagents available.[50] On the practical side, the phenylseleno group contributes to a high molecular weight, which is desirable when removing solvents under vacuum. It also renders the compounds visible under the U.V.lamp, a property which is convenient when examining thin layer chromatography plates. A problem frequently encountered in the use of stannanes for the generation of the radical, is the removal of the resulting tin species, which in this case is a tin-selenide compound. However, in all the cases described here, the products of cyclization could be separated from the tin residues by simple flash chromatography of the crude reaction product.

Radical Source in the Diene

The first experiments conducted involved the use of a diene that contained the radical source, according to Scheme 15, entry (a). Diene **143** was the first one that was made since the corresponding alcohol **142** was a known compound derived from sorbyl alcohol (eq. 56).[51]

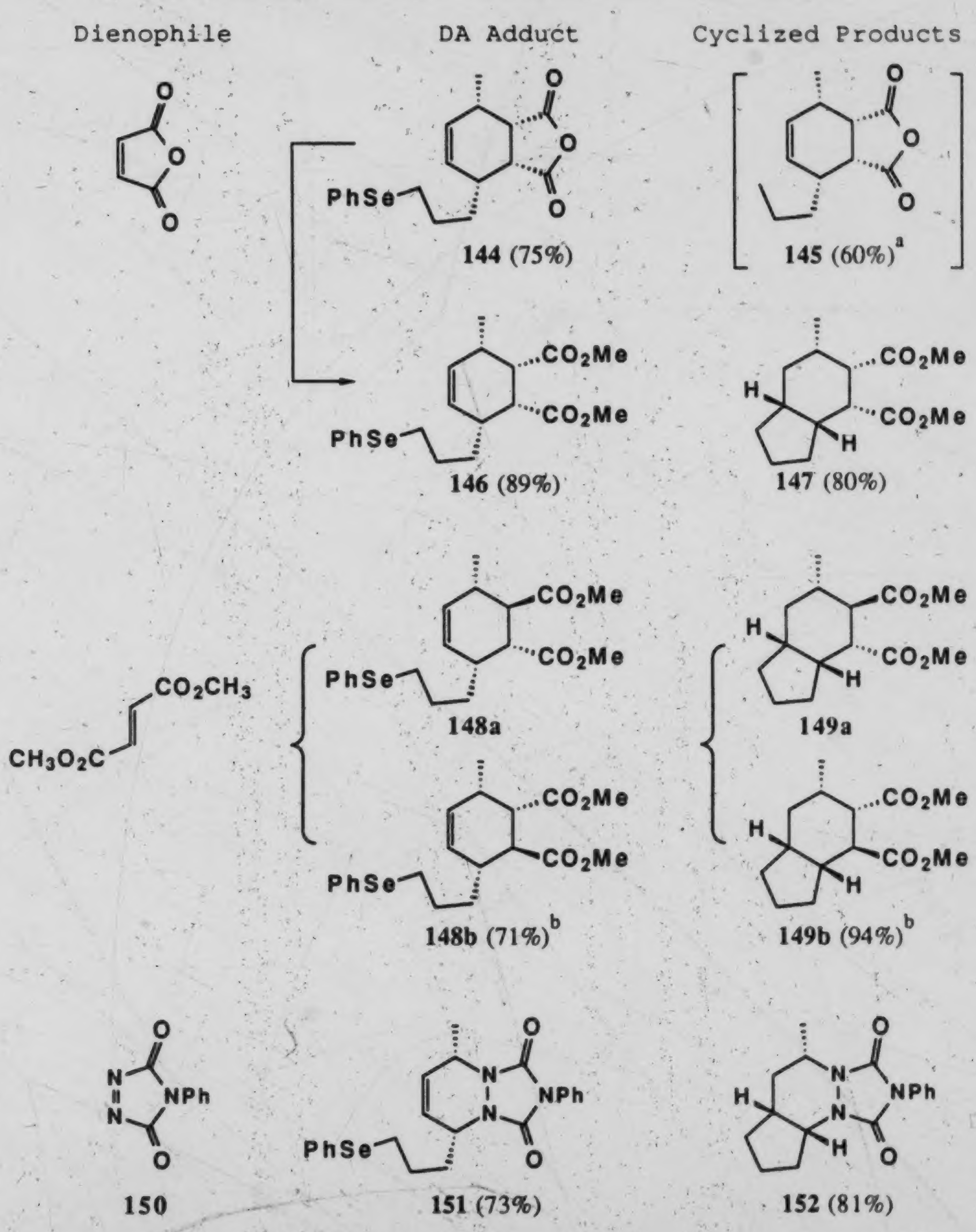


Conversion of the hydroxyl group to a selenide was effected with phenylselenocyanate (PhSeCN) and tributylphosphine.[52] Alternatively, one can make the tosylate and carry out a displacement with selenide anion. This second procedure is preferable for a large scale reactions, due to the high toxicity and the extreme foul odour of both PhSeCN and the phosphine. Compound **143** did contain a small amount (<10%) of another isomer that was detected in the NMR spectra. It was established that the corresponding isomer was also present in alcohol **142** but *not* in the sorbyl alcohol. [The literature preparation was followed, but no mention was made of any minor isomers.] Purification of **142** was attempted by spinning band distillation and by recrystallization of its 3,5-dinitrophenylbenzoate, but neither procedure proved fruitful. In any event, the presence of another isomer did not pose any problems, as in subsequent steps, pure compounds were easily obtained.

Diene **143** was reacted with several dienophiles and the results are shown in Table 3.

TABLE 3

Diels-Alder/Radical Closure Using Diene **143**


Dienophile
DA Adduct
Cyclized Products
PhSe
144 (75%)
145 (60%)[a]
PhSe
146 (89%)
147 (80%)
CO2Me
CO2Me
H
H
CO2CH3
CH3O2C
PhSe
148a
149a
PhSe
148b (71%)[b]
149b (94%)[b]
NPh
150
PhSe
151 (73%)
152 (81%)

[a] A small amount (16%) of the desired cyclized material was detected by ^{1}H NMR spectroscopy. [b] Combined yield. 148a:148b = 1:1. [c] Combined yield. 149a:149b = 1:1.

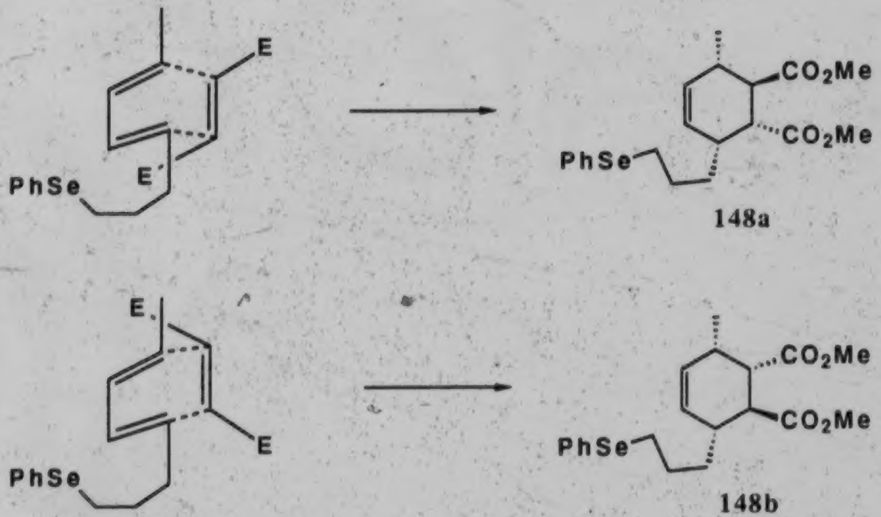
Compound **144** was obtained by refluxing a benzene solution of **143** and maleic anhydride, the pure all *cis*-substituted cyclohexene being obtained in good yield. Radical ring closure was attempted with the use of triphenyltin hydride. This choice of stannane was based primarily on tradition in this laboratory. In the past, it had been found convenient to use triphenyltin hydride (as opposed to tributyltin hydride) mainly because the presence of any tin residues in the product would easily be seen at low field in the ^{1}H NMR spectrum, remote from the peaks corresponding to the desired compound. In addition, satisfactory results were generally obtained with triphenyltin hydride. Tributyltin hydride is a poorer hydrogen donor[†] and, in principle, is a better choice for avoiding reduction prior to cyclization, but for the reaction conditions reported here (*vide infra*) no advantage was observed by its use..

Radical cyclization of **144** did not proceed well, as only the reduced starting material **145** was isolated (which is the result of hydrogen capture prior to cyclization). The integration of the ^{1}H NMR spectrum indicated the presence of approximately 16% of a cyclized product, but this compound was not isolated or characterized. The presence of **145** was easily deduced from the spectrum by the presence of a high field triplet (corresponding to a terminal methyl group) and signals corresponding to olefinic hydrogens. It is not clear from Dreiding models why **144** does not undergo efficient ring closure, but less rigid analogues were found to react in the desired way (*vide infra*). Ring opening of the anhydride by refluxing **144** in acidic methanol, produced the more conformationally mobile diester **146**. It was determined that no epimerization of the carboxylate groups had occurred, since the reaction produced a single isomer, and the coupling patterns of the protons *alpha* to the carbonyls were very similar to those of the parent anhydride. Radical closure of **146** proceeded as desired, producing the *cis*-fused 6-5 system in 80% yield. Some reduced starting material was detected by ^{1}H NMR spectroscopy of the crude reaction mixture, but this compound was not isolated.

[†] $D°(Bu_3Sn\text{-}H) = 74$ kcal/mol, $D°(Ph_3Sn\text{-}H) = 68$ kcal/mol.

Diels-Alder reaction of **143** with dimethyl fumarate was effected in refluxing xylene, to give an inseparable mixture of two diastereomers (Fig. 4). Compound **148a** results from the carbonyl of the fumarate being *endo* to the alkyl side chain in the transition state, and **148b**, from the carbonyl being *endo* to the methyl group.

This mixture was subjected to the radical cyclization conditions, and a 94% yield of the expected *cis*-fused[30b] compounds **149a** and **149b** was obtained, again, as an inseparable pair of diastereomers.



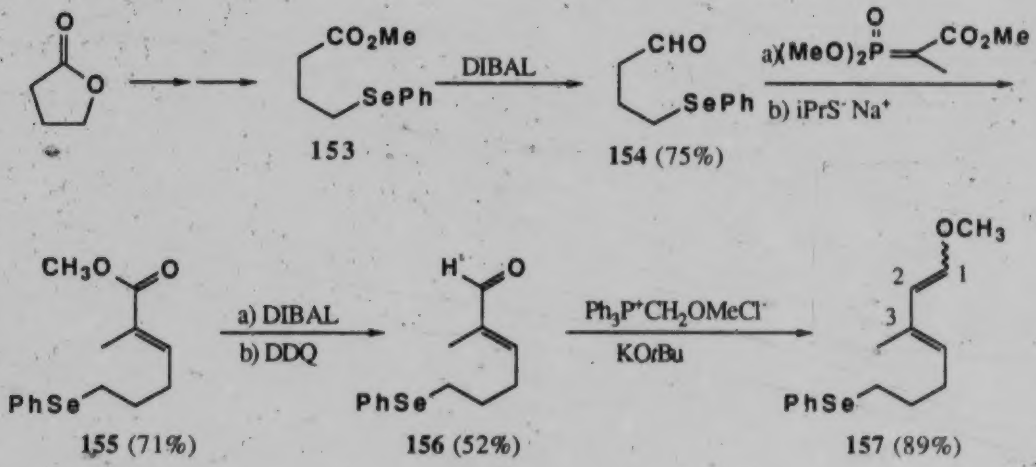
148a

148b

Fig. 4 Transition state for the formation of **148a** and **148b** (E = COOMe)

Diene **143** was also treated with the triazolinedione **150**,[53] which is one of the most reactive dienophiles known, and this sequence proceeded without incident to the tricyclic heterocycle, **152**. The ability of **151** to cyclize stands in contrast to the attempted ring closure of **144**. It should be noted that there is a higher degree of conformational mobility in **151**.

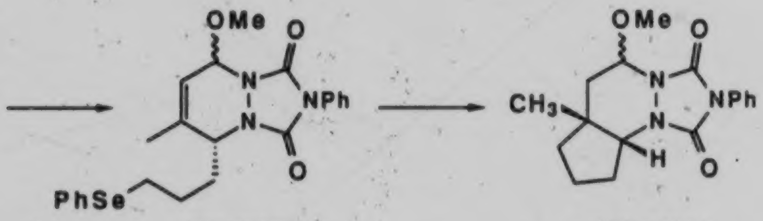
One of the advantages of radical reactions is their lower sensitivity to steric effects as compared to corresponding ionic reactions. Therefore we wanted to provide an example of a radical ring closure onto a fully substituted double bond. It was decided to make diene **157**, with a methoxy group at C(1) (as opposed to the unsubstituted version) because of the added advantage that this would introduce additional functionality in the Diels-Alder adduct. If necessary, the methoxy group would allow activation[54] of the olefin towards radical addition by oxidation to an enone system (*vide infra*). Diene **157** also contains a methyl group at C(3), the position at which cyclization would ultimately occur, and was prepared as a mixture of isomers as described in eq. 57.


CO2Me
SePh
153
DIBAL
CHO
SePh
154 (75%)
a) (MeO)2P(O)=C(CH3)CO2Me
b) iPrS⁻ Na⁺
CH3O
O
PhSe
155 (71%)
a) DIBAL
b) DDQ
H
O
PhSe
156 (52%)
Ph3P⁺CH2OMeCl⁻
KOtBu
OCH3
1
2
3
PhSe
157 (89%)

eq. 57

Selenoester **153** is a known compound available via the selenide promoted ring opening of butyrolactone.[55] Reduction to the aldehyde **154** and subsequent Horner-Emmons reaction[56] with methyl α-(dimethylphosphono)propionate,[57] gave ester **155** as a mixture of *cis* and *trans* isomers, that was equilibrated with isopropylthiolate[58] to *trans* **155**, containing the desired methyl group. Conversion of **155** to the corresponding aldehyde **156** was affected by DIBAL reduction (which is known to reduce α,β-unsaturated esters to allylic alcohols)[59] followed by DDQ oxidation.[50a] A Wittig reaction with (methoxymethyl)triphenylphosphonium chloride[60] provided the required diene **157** as a mixture of isomers. Treatment of **157** with the triazolinedione **150**, followed by radical closure, indeed, afforded the *cis*-fused tricyclic system **159** containing an angular methyl group (eq. 58). However, since **157** was quite unreactive with other more conventional dienophiles (i.e. acrylate, maleic anhydride, *p*-benzoquinone), it was decided to make, in addition to **157**, the corresponding silyloxy butadiene, which is of a compound class known to be more reactive.

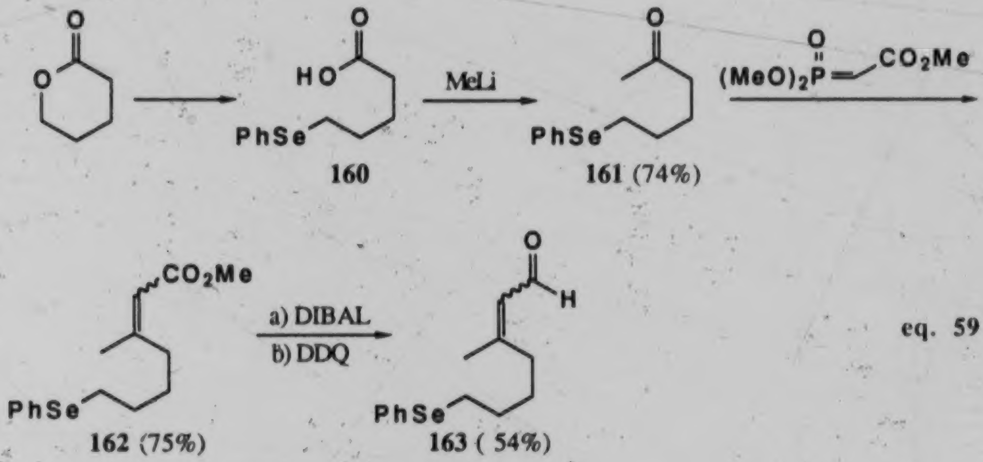
157



158 (73%) **159** (77%)

eq. 58

Silyloxy butadienes are generally constructed by enol ether formation from the corresponding α,β-unsaturated aldehydes, and so aldehyde **163** was prepared according to eq. 59. Acid **160** is a known compound derived from the ring opening of valerolactone,[55] and addition of methyllithium[61] installed the desired methyl group, giving ketone **161**. Horner-Emmons reaction produced a mixture of *cis* and *trans* esters **162**, which was not isomerized, since the geometry of the double bond is probably irrelevant for the enolization step. Compound **162** was converted to the corresponding aldehyde **163** as before.

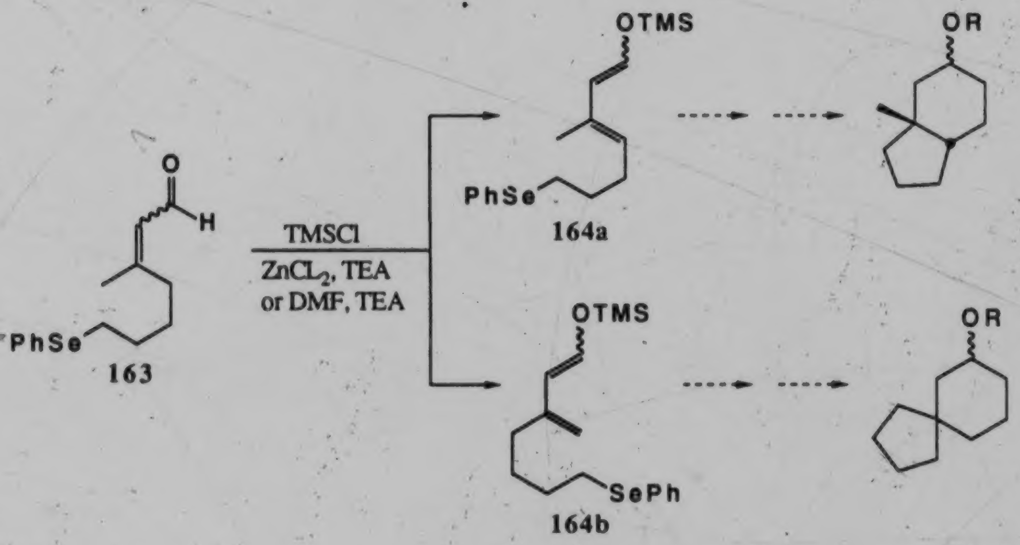


eq. 59

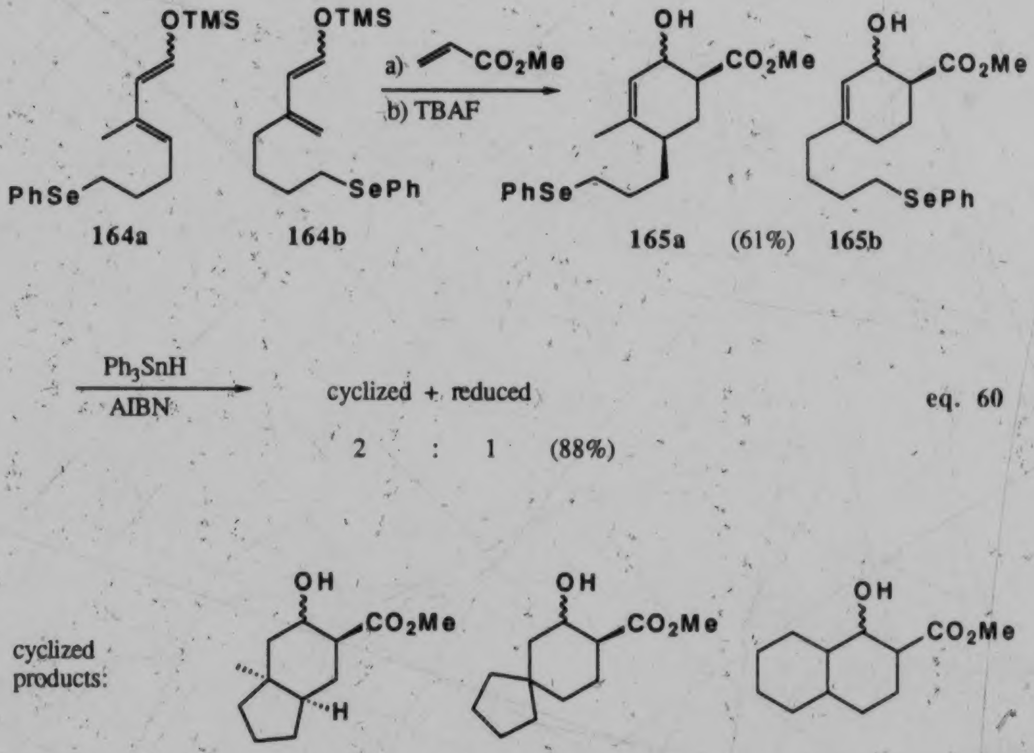
However, when **163** was treated with TMSCl and either $ZnCl_2$/TEA[62] or DMF/TEA,[63] an inseparable mixture of isomeric butadienes was obtained, **164a** resulting from thermodynamic deprotonation of the methylene group, and **164b** from kinetic deprotonation of the methyl group (Scheme 16). Both dienes are of interest for the Diels-Alder/radical cyclization methodology since **164a** would produce a compound with an angular methyl group (analogous to **157-->159**), and **164b** would lead, ultimately, to the formation of a spiro compound.

However, the mixture of **164a** and **164b** proved to be problematic, since the compounds could not be separated by flash chromatography as they are unstable to silica, and attempts to form diene **164b** at low temperature, via kinetic deprotonation, were unsuccessful. Consequently, the compounds were dealt with as a mixture, since the products of the cyclization step should be identifiable by ^{1}H NMR spectroscopy without prior separation.

SCHEME 16


O
H
PhSe
163
TMSCl
$ZnCl_2$, TEA
or DMF, TEA
OTMS
PhSe
164a
OR
OTMS
SePh
164b
OR

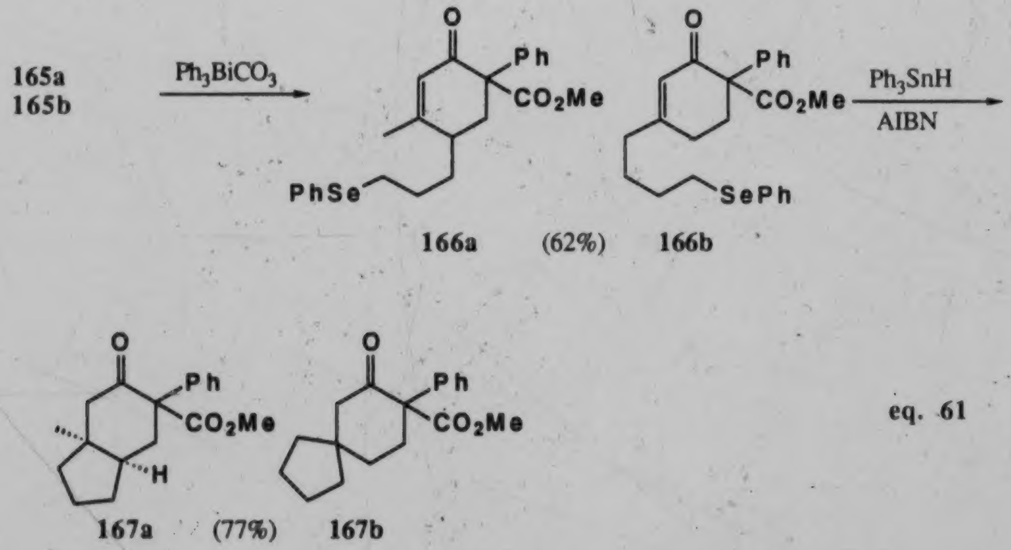
The Diels-Alder adducts with methyl acrylate were obtained (eq. 60). After hydrolysis the resulting mixture of alcohols **165a** and **165b** was treated with stannane to give a complex mixture of products (88% yield) that were inseparable by flash chromatography. However, it was determined from the ^{1}H NMR spectrum that approximately 65% of the product was cyclized material, presumably corresponding to some or all of the bicyclic compounds shown in equation 60.


OTMS
OTMS
PhSe
SePh
164a
164b
a) CO2Me
b) TBAF
OH
CO2Me
PhSe
165a
(61%)
OH
CO2Me
SePh
165b
Ph3SnH
AIBN
cyclized + reduced
2 : 1 (88%)
cyclized products:
OH
CO2Me
H
OH
CO2Me
OH
CO2Me

eq. 60

In order to increase the rate of ring closure of compounds **165**, and at the same time decrease the number of isomers, attempts were made to oxidize the hydroxyl group to a ketone, so that radical addition could occur in a Michael fashion. As mentioned earlier, due to the presence of the selenide, there are limitations in the choice of oxidizing agents.[50] Chromate-based oxidants would attack the selenide, and DDQ, manganese dioxide and standard Swern or Corey-Kim conditions all gave no reaction.

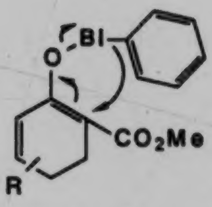
Barton's triphenylbismuth carbonate reagent,[50b] was the only reagent that oxidized the alcohols **165**, but it also delivered a phenyl group to the position *alpha* to the two carbonyls affording enones **166a** and **166b** as an inseparable mixture* (eq. 60). Presumably this reaction goes through transition state **166'** (Fig. 5). This side reaction occurs with a variety of triphenylbismuth reagents.[64]


165a
165b
Ph3BiCO3
O
Ph
CO2Me
PhSe
O
Ph
CO2Me
SePh
Ph3SnH
AIBN
166a
(62%)
166b
O
Ph
CO2Me
H
O
Ph
CO2Me
167a
(77%)
167b

eq. 61

---

*The stereochemistry of **166a** and **167a** was not determined, but each compound was a single isomer (^1H NMR spectroscopy).

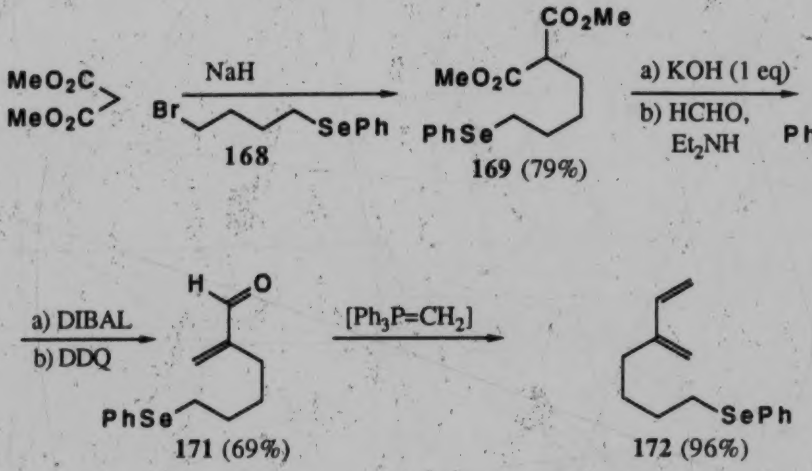


166'

Fig. 5 Phenylation of keto ester

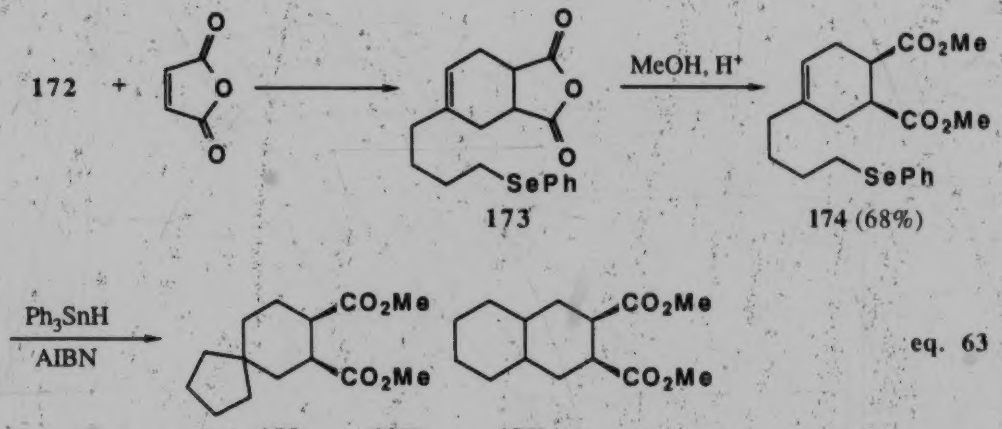
The presence of the phenyl group did not perturb the system in any way, as cyclization proceeded in 77% yield to give a mixture of compounds **167a** and **167b** (eq. 61). The presence of a methyl singlet in the ^1H NMR spectrum of the product mixture indicated the presence of **167a**. The absence of any reduction products allowed, by default, the structural assignment of **167b** to be the expected spiro compound.

The ring closure observed with Diels-Alder adduct **165b** prompted investigation of a different route for synthesis of a diene of the general structure of **164b**, that would be uncomplicated by the presence of isomers. The simplest example is diene **172**, which was constructed according to eq. 62. Bromo selenide **168** was derived from 1,4-dibromobutane by a similar procedure to that which has since appeared in the literature,[40b] and was used to alkylate dimethyl malonate. The resulting compound **169** was then converted, according to a known procedure,[65] to the α-methylene ester **170**, via formation of the half ester, followed by a Mannich reaction with formaldehyde. Using the same reaction sequence as before, **170** was transformed to aldehyde **171**, and Wittig reaction with methyltriphenylphosphonium chloride produced the desired diene **172**.


MeO2C
MeO2C
NaH
Br
SePh
168
CO2Me
MeO2C
PhSe
169 (79%)
a) KOH (1 eq)
b) HCHO, Et2NH
CO2Me
PhSe
170 (44%)
a) DIBAL
b) DDQ
H
O
PhSe
171 (69%)
[Ph3P=CH2]
SePh
172 (96%)

eq. 62

The cycloaddition of **172** to maleic anhydride afforded the expected adduct **173** (eq. 63). Unlike compound **144**, this anhydride was unstable to silica, and therefore it was necessary to convert it to the dimethyl ester **174**. Treatment of **174** with triphenyltin hydride afforded a near quantitative yield of an inseparable mixture of two compounds, as determined from the ^{13}C NMR spectrum by the presence of four separate peaks at ~174 ppm corresponding to carbonyl carbons. The absence of a high field triplet in the ^{1}H NMR spectrum indicated that all the material was cyclized. An attached proton test (APT spectrum) indicated (among other things) the presence of an additional two carbons that were either 1° or 3° that would *not* be present in a stereoisomer of the desired spiro structure. Based on this spectral data, the compounds are assigned structures **175a** and **175b**, the latter resulting from 6-*endo* closure. The stereochemistry of the decalin system **175b** was not determined, but the compound was obtained as a single isomer, as determined by ^{13}C NMR spectroscopy.

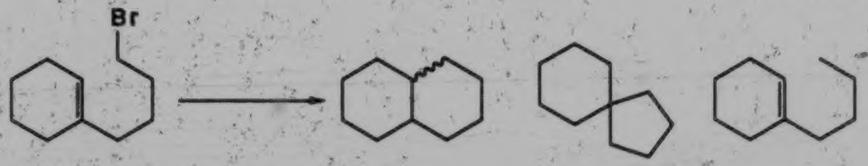

172
+
O
O
O
O
O
O
SePh
MeOH, H+
CO2Me
CO2Me
SePh
Ph3SnH
AIBN
CO2Me
CO2Me
CO2Me
CO2Me

173 174 (68%)

175a (99%) 175b

eq. 63

The products of cyclization in eq. 63 are also consistent with related studies by Beckwith[5] involving 1-(4-bromobutyl)-cyclohexene (eq. 64), in which case both *exo* and *endo* closure was observed. We did not observe any reduction product due to the use of tin hydride at low concentration (see Experimental section).

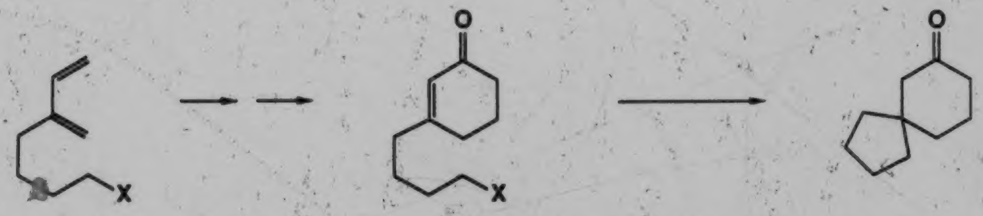


28% 35% 36%

eq. 64

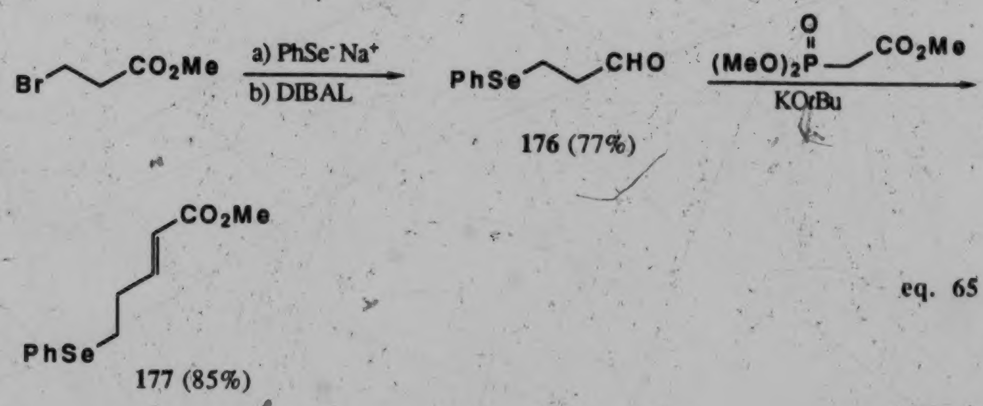
The outcome of the ring closure of **174** does confirm that for efficient 5-*exo* closure to produce a spiro compound, the olefin must be activated with an electron withdrawing group. Construction of a spiro compound via the route shown in Scheme 17 was not pursued further as access to the required enone intermediate was difficult, as described above.

SCHEME 17



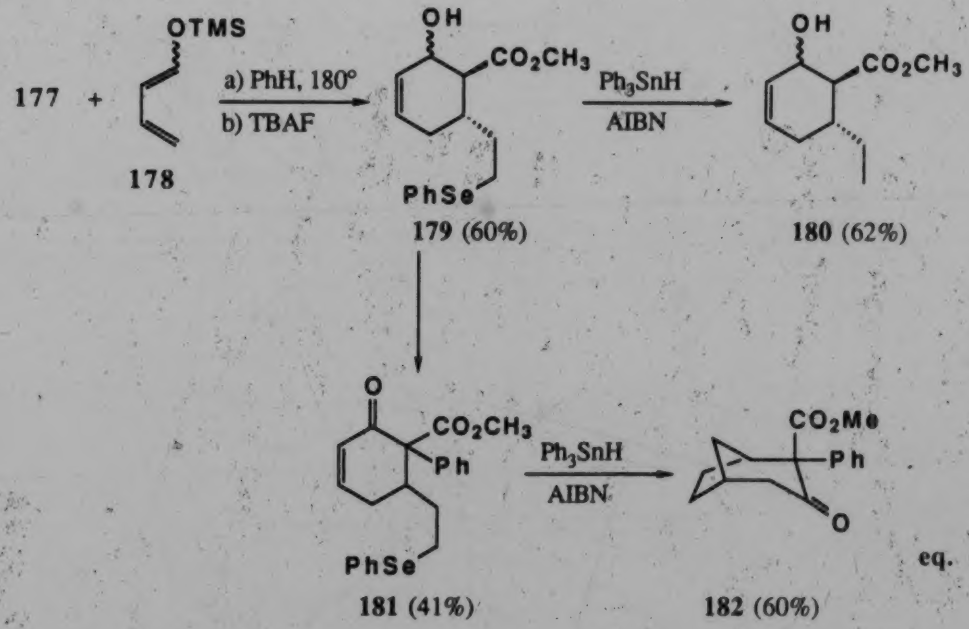
Radical Source in the Dienophile.

The initial purpose of using a dienophile that contained the radical source was to develop a route to a bridged compound, along the lines of Scheme 15, entry b, and this required the synthesis of α,β-unsaturated ester **177**. This compound is readily available via Horner-Emmons reaction with aldehyde **176**, which, in turn is derived in two steps from methyl 3-bromopropionate (eq. 65).


Br
CO2Me
a) PhSe- Na+
b) DIBAL
PhSe
CHO
176 (77%)
O
(MeO)2P
CO2Me
KOtBu
CO2Me
PhSe
177 (85%)

eq. 65

The Diels-Alder adduct with the 1-silyloxy butadienes **178** was obtained as a mixture of isomers and in moderate yield by heating (180°C) a benzene solution of the reactants in a sealed tube for 36 hours (eq. 66).


177
+
OTMS
178
a) PhH, 180°
b) TBAF
OH
CO2CH3
PhSe
179 (60%)
Ph3SnH
AIBN
OH
CO2CH3
180 (62%)
O
CO2CH3
Ph
PhSe
181 (41%)
Ph3SnH
AIBN
CO2Me
Ph
O
182 (60%)

eq. 66

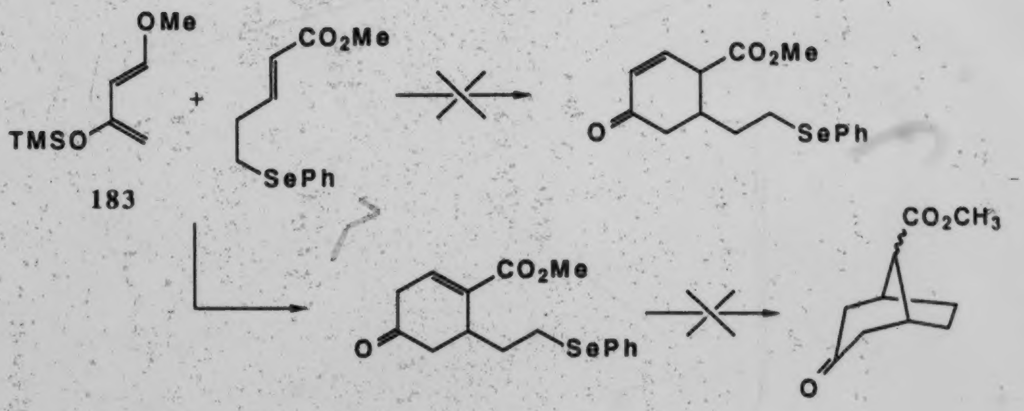
Hydrolysis of the initial cycloadduct resulted in a mixture of alcohols **179** that was subjected to the cyclization conditions. However, the presence of a high field triplet in the ^1H NMR spectrum of the reaction product indicated that very little cyclization had occurred, giving structure **180**. Therefore, in accordance with the previous findings, **179** was oxidized to the cyclohexenone using Barton's reagent, and as in the previous case (see **165-->166**), a phenyl group was delivered to the position *alpha* to the carbonyls.* Now cyclization of **181** occurred in a 5-*exo* Michael fashion and the [3.2.1] bicyclic compound **182** was obtained in 60% yield.

The necessity to activate the olefin of **179** by oxidation to the enone prompted the use of Danishefsky's diene, 1-methoxy-3-(trimethylsilyloxy)butadiene **183**,[62] which, after hydrolysis of the Diels-Alder adduct, produces cyclohexenones directly. However, it is not possible to construct a bridged compound via the route shown in Scheme 18. The presence of the ester functionality causes the double bond to move to the more substituted position and cyclization is disfavoured because the process would involve 5-*endo* closure.

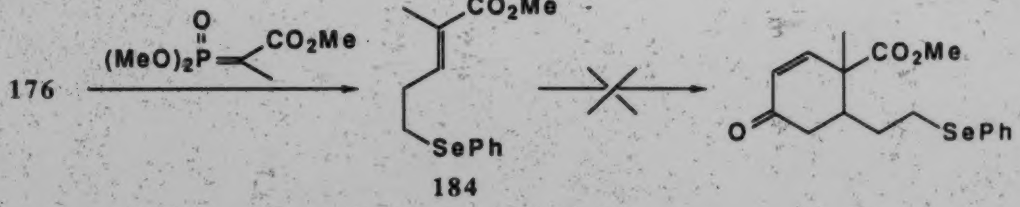
---

*The stereochemistry of compounds **181** and **182** was not established, but they both were one major isomer as determined by ^1H NMR spectroscopy.

SCHEME 18

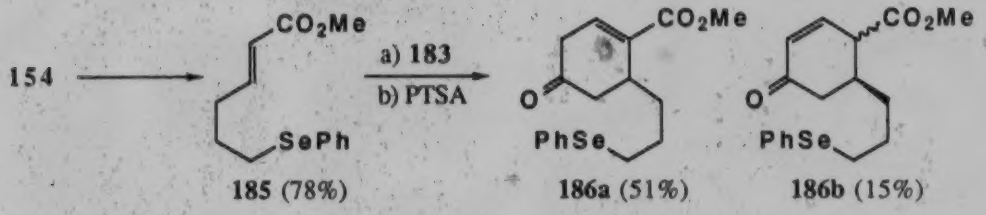

OMe
TMSO
+
CO₂Me
SePh
183
CO₂Me
O
SePh
CO₂Me
O
SePh
CO₂CH₃
O

In light of this, ester **184** was constructed (eq. 67) by the previously established route. The methyl group at C(2) would prevent the double bond in the cyclohexenone from shifting into conjugation with the ester. Thus the system would be set up for 5-*exo* closure to the desired bridged structure.


176
O
(MeO)₂P
CO₂Me
CO₂Me
SePh
184
CO₂Me
O
SePh

eq. 67

Unfortunately, heating a benzene solution of diene **183** and ester **184** in a sealed tube at 200°C did not lead to any cycloadduct. The next alternative was to change the length of the selenide-bearing carbon chain to facilitate an allowable ring closure other than 5-*exo*. This approach required the synthesis α,β-unsaturated ester **185**, which is readily available from aldehyde **154**. Ester **185** has a longer alkyl chain, so that radical cyclization could occur also for **186a** (eq. 68), i.e., in a 6-endo Michael fashion. Diels-Alder reaction of **185** with diene **183** afforded, after hydrolysis, a mixture of compounds, the major one being **186a** (eq. 68).



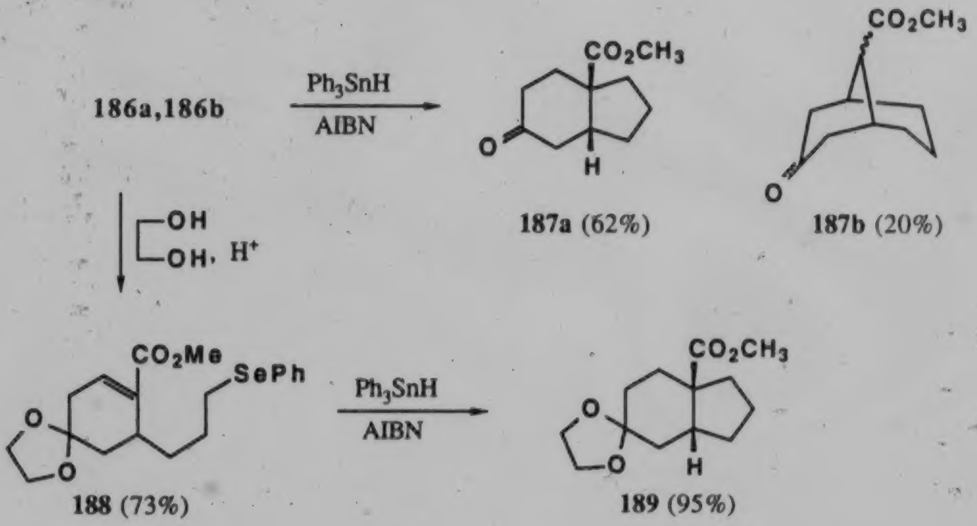
eq. 68

However the radical cyclization reaction did not go as anticipated. Treatment with stannane (Scheme 19) produced primarily **187a** arising from 5-*exo* closure, along with some of the desired bridged compound **187b** that was assumed to be derived from **186b** since the ratio of the products was similar to that of the starting materials. To clarify this result, the mixture of ketones **186a** and **186b** was converted to acetal

188, by treatment with acidic ethylene glycol.[62b] The double bond moved exclusively into conjugation with the ester and radical ring closure then gave solely the 5-*exo* anti-Michael product **189**. This confirms that none of the bridged compound formed in the cyclization of **186a** and **186b** came from 6-*endo* Michael closure of **186a**.

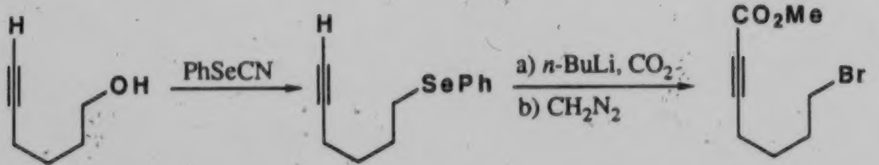
These results prompted us to examine the potential for electron withdrawing groups in promoting 6-*endo* closure over 5-*exo* (*vide infra*).

SCHEME 19



186a,186b
Ph3SnH
AIBN
CO2CH3
O
H
187a (62%)
CO2CH3
O
187b (20%)
OH
OH, H+
CO2Me
SePh
O
O
188 (73%)
Ph3SnH
AIBN
CO2CH3
O
O
H
189 (95%)

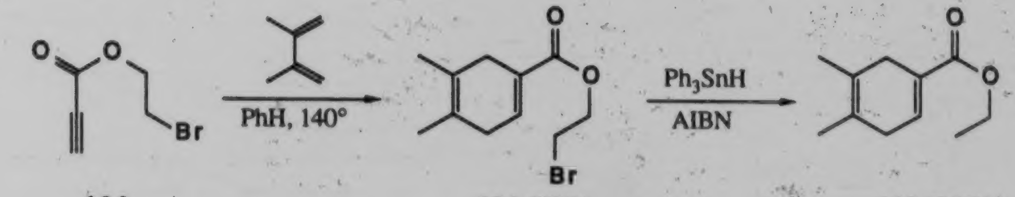
Acetylenes are known to act as dienophiles if they are activated by a sufficiently strong electron-withdrawing group and therefore they have good potential for the extension of the Diels-Alder/radical cyclization reaction sequence. The first acetylenic dienophile made was ester **192**, in the interest of producing a spiro compound according to Scheme 15, entry c. This compound is readily available from commercial 5-hexyne-1-ol **190** (eq. 69). Treatment with phenylselenocyanate converted the alcohol **190** to selenide **191**; deprotonation, addition of carbon dioxide, followed by treatment with diazomethane, produced the selenoester **192**.



eq. 69

190 **191** (54%) **192** (85%)

However, the ester functionality is not sufficiently activating for substituted acetylenes to act as dienophiles, as attempts at cycloaddition with a number of dienes [1-acetoxy-, 1-methoxy-, and 1-(trimethylsilyloxy)butadienes] were unsuccessful. On the other hand, unsubstituted propiolate esters are more reactive, and are known to undergo thermal Diels-Alder reactions,[48] and so 2-bromoethyl propiolate **193** was made. Compound **193** was heated with dimethyl butadiene in a sealed tube, and the expected cylcohexadiene **194** was obtained (eq. 70). However, attempted radical cyclization resulted only in reduction product **195**.



193

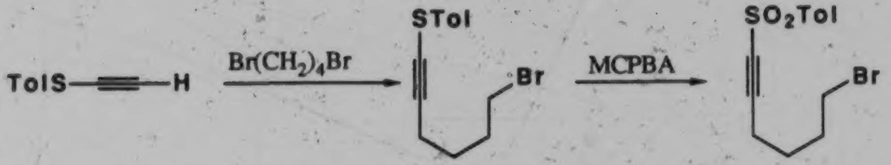
194 (83%)

195 (83%)

eq. 70

In comparing this result with the cyclization of **174** one may have expected 6-*endo* Michael closure (some was obtained in the other case, and here the double bond is activated). However, it would appear that the presence of oxygen in the potential ring being formed is not compatible with this process, and therefore this result is in agreement with the low rate of 6-*endo* closure for the 3-oxa-5-hexenyl radical.[5] It is not clear why 5-*exo* closure was not observed.

For substituted acetylenes, a sulfone is sufficiently activating for purposes of Diels-Alder reactions.[66] With this in mind, acetylenic sulfone **197** was synthesized by alkylation of tolylthioacetylene[67] with 1,4-dibromobutane, followed by oxidation with *m*-chloroperbenzioc acid (eq. 71).[68]

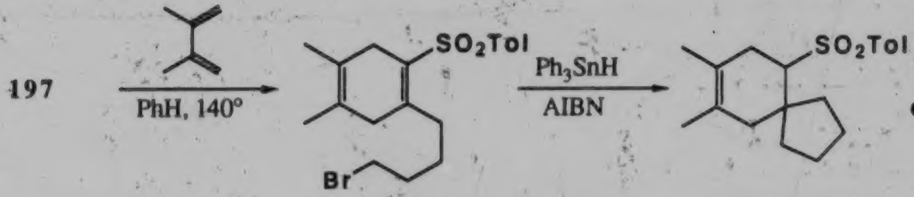


196 (32%)

197 (92%)

eq. 71

Sulfone **197** was heated with 2,3-dimethyl butadiene in a sealed tube, providing cyclohexadiene **198**. 5-*Exo* closure would lead to the desired spiro compound, and indeed, addition of triphenyltin hydride afforded **199**, in 61% yield (eq. 72).



198 (83%)

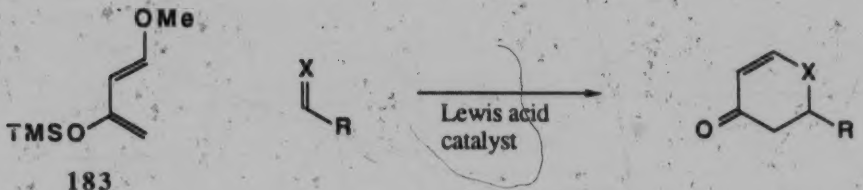
199 (61%)

eq. 72

Hetero Diels-Alder Reactions

We then turned our attention to the use of radical cyclization in conjunction with the hetero Diels-Alder reaction. Danishefsky has shown that diene **183** will condense, in the presence of a Lewis acid, with both aldehydes[69] and imines[70] (Scheme 20).* We intended to apply this technology using an aldehyde or imine that contained the radical source, a strategy which would produce a structure similar to that shown in Scheme 15, entry b, but containing a heteroatom in the smallest bridge.

SCHEME 20

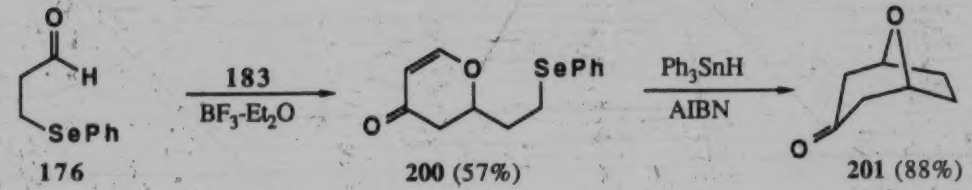


183

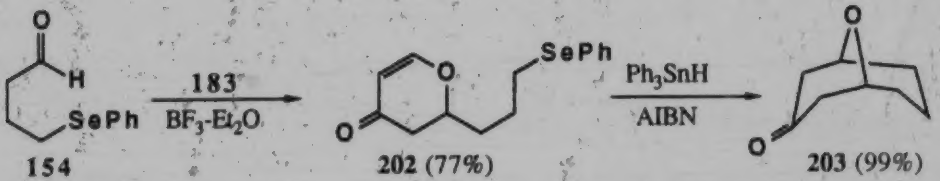
X = O, NR

This approach required a 3-substituted aldehyde and, since **176** was already in hand from previous studies, it was used as the starting material and treated according to Scheme 20. The cycloaddition product **200** was obtained, using boron trifluoride etherate as the catalyst (eq. 73),[69] and radical cyclization produced the [3.2.1] oxabicyclic compound **201**.

*The exact mechanism of the cycloaddition is not known. It is formally a Diels-Alder reaction, but it is doubtful that it has a concerted mechanism.

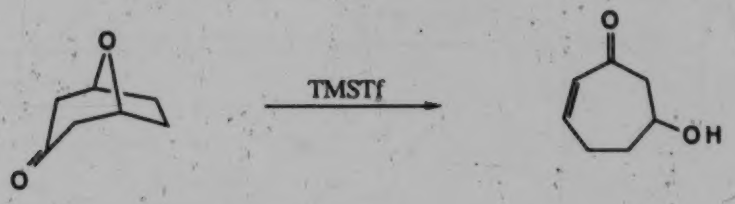

SePh
H
176
183
BF3-Et2O
SePh
200 (57%)
Ph3SnH
AIBN
201 (88%)

eq. 73

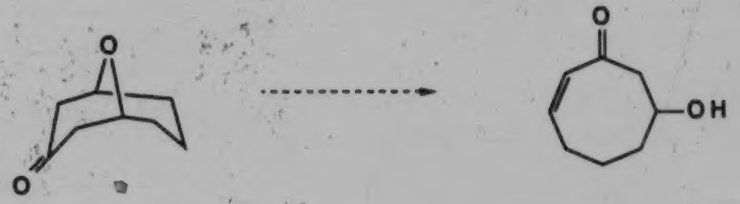

H
SePh
154
183
BF3-Et2O
SePh
202 (77%)
Ph3SnH
AIBN
203 (99%)

eq. 74

The substituted butyraldehyde **154** was treated along the same lines (eq. 74), and in this case 6-*exo* closure produced the [3.3.1] oxabicyclic compound **203**. The 6-*exo* process was particularly efficient by virtue of the fact that radical addition to the activated olefin occurred in a Michael fashion. In both cases **201** and **203**, the symmetry of the compounds was clearly reflected in the NMR spectra. Ketone **201** is a known compound[71] that had been used for the synthesis of a seven-membered ring via cleavage of the ether using trimethylsilyltriflate (eq. 75).[71b] In light of this work, the methodology shown in eq. 74 may be useful in the synthesis of eight-membered ring compounds (eq. 76), but we have not examined the possibility.


O
TMSTf
O
O
OH

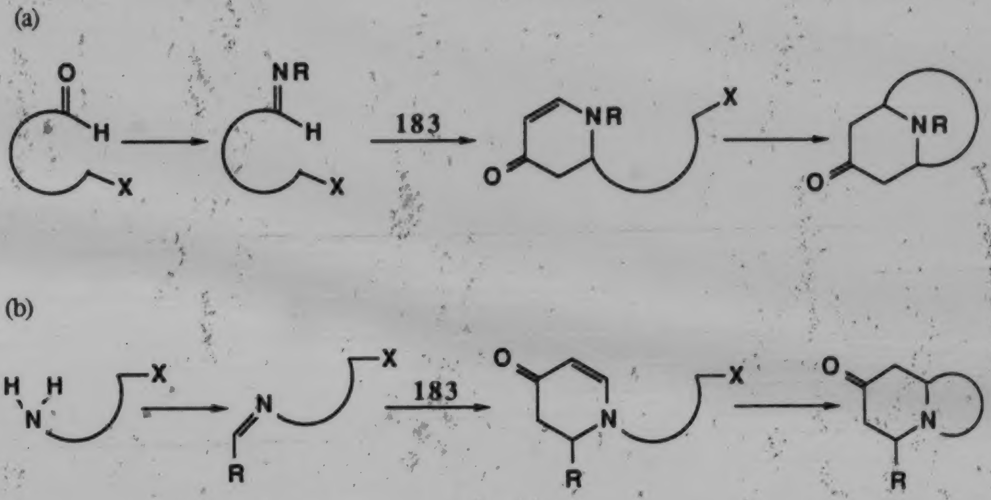
eq. 75



eq. 76

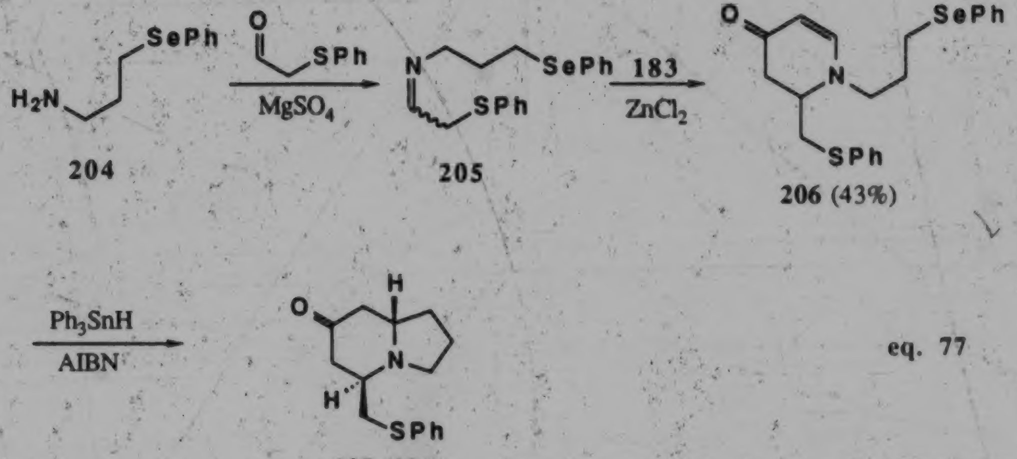
The reaction sequence of eq. 73 and 74 can also be conducted using imines as the dienophile. The required imines may be of two types, in the sense that either the aldehyde or the amine can carry the radical precursor, and the potential for this chemistry is outlined in Scheme 21.

SCHEME 21


(a)
O
H
X
NR
H
X
183
NR
X
O
NR
O
(b)
H H
N
X
N
X
R
183
O
N
X
R
O
N
R

If the aldehyde were to carry the radical source [entry (a)], then the product after ring closure would be a nitrogen heterocycle analogous to the bridged ethers, **201** and **203**. Such bridged structures represent the tropane class of alkaloids, whose molecular framework is readily available by other methods,[72] and so we decided to concentrate on the linearly fused system [entry (b)] which results from imines derived from amines carrying the radical source. The 6-5 system represents the indolizidines, and the 6-6 system the quinolizidines. Both are substructures of a large number of alkaloids (*vide infra*).[73]

A simple case in this series involves amine **204**, which is a known compound.[40a] Imine formation with acetaldehyde was not successful, and so, based on the observations of Danishefsky,[69b] (phenylthio)acetaldehyde[74] was used (eq. 77). The required imine **205** was assembled by simply mixing **204**, with the aldehyde in the presence of a drying agent (magnesium sulfate). Cycloaddition was achieved,[70] by treatment of **205** with an excess of the diene **183**, in the presence of zinc chloride, affording vinylogous amide **206**. Treatment with triphenyltin hydride provided the indolizidine **207a** in good yield.



204 205 206 (43%)

207 (83%)

eq. 77

A unique spectral feature concerning structures of this type is the appearance of Bohlmann bands in the IR spectrum.[75] This is a peak found at approximately 2800 cm^{-1} that represents a C-H stretch antiperiplanar to the nitrogen lone pair. Therefore indolizidines that exhibit strong Bohlmann bands have the maximum number (3) of hydrogens bearing such a relationship to the nitrogen lone pair.

Compound **207a** did not show such bands and this is in agreement with the assigned *syn* stereochemistry of the PhSCH$_2$ group and the bridgehead hydrogen *and* the *cis*-fused conformation shown in Fig. 6. In principle, the compound could adopt the conformation of **207a'**, but this structure would show Bohlmann bands, and it also has the phenylthiomethyl group in an unfavourable axial position.

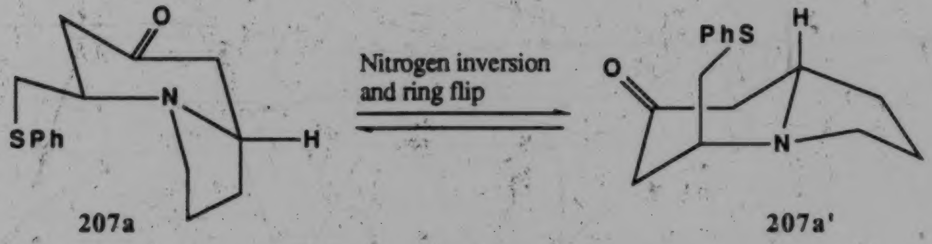
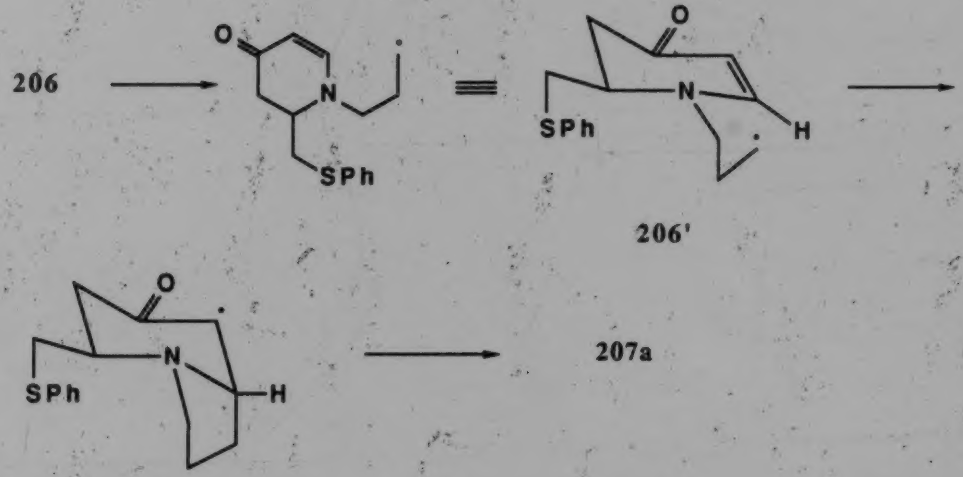

O
SPh
N
H
Nitrogen inversion
and ring flip
PhS
H
O
N
207a
207a'

Fig. 6 Conformation of indolizidine **207a**

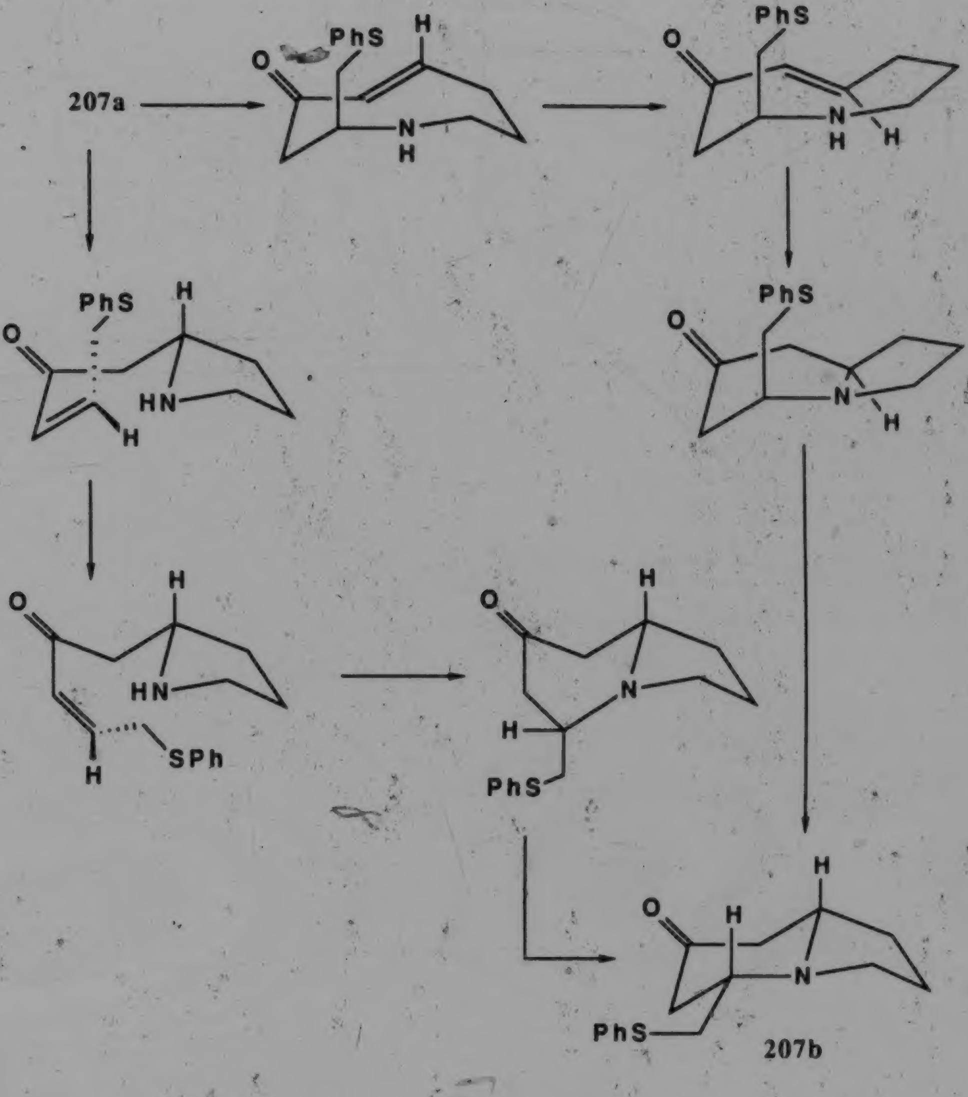
The stereochemical assignment is also consistent with transition state **206'** (Scheme 22) which invokes axial attack of the radical with both pendants equatorial.

SCHEME 22


206
O
N
SPh
O
SPh
N
H
206'
O
SPh
N
H
207a

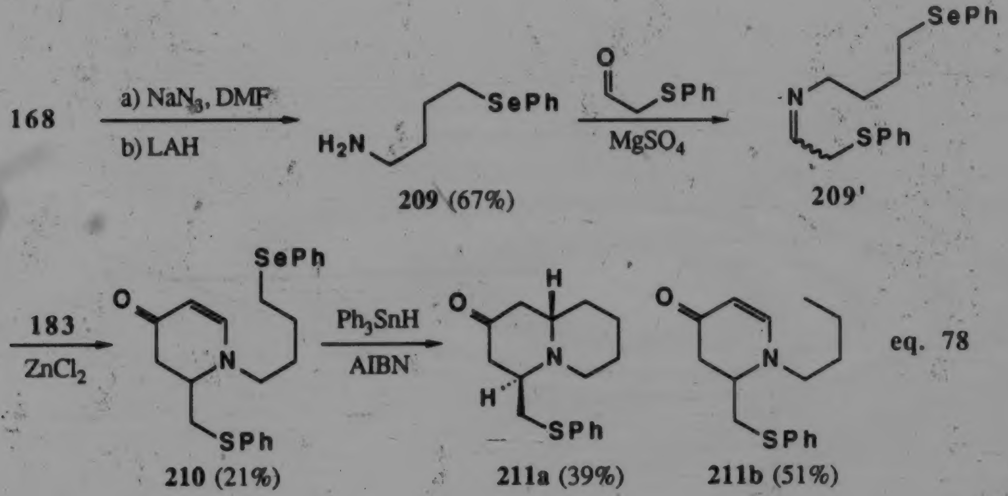
Upon standing at room temperature for several days, compound **207a** isomerized to stereoisomer **207b** that *did* exhibit strong Bohlmann bands. Presumably the isomerization occurred via the base catalysed (auto catalysis) mechanism shown in Scheme 23.

SCHEME 23


207a
PhS
O
H
N
SPh
HN
207b

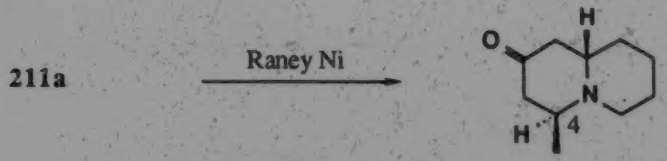
This was a significant observation since it shows that that if we were to synthesize the gross structure of an indolizidine alkaloid, then an isomerization step to the more product of radical closure does not necessarily have to have the stereochemistry of the target molecule.

An attempt to extend the scope of the Diels-Alder/radical cyclization methodology, to the synthesis of the quinolizidine framework by a 6-*exo* cyclization, was not as successful. This attempt required the use of 4-(phenylseleno)butylamine **209**, which is a known compound.[40a] However, we made it by a different route, starting with bromo selenide **168**, by reduction of the corresponding azide (see Experimental, compound **208**). Imine formation, and cycloaddition was performed as before to produce **210** in low overall yield (eq. 78).


168
a) NaN3, DMF
b) LAH
H2N
SePh
209 (67%)
O
SPh
MgSO4
N
SePh
SPh
209'
183
ZnCl2
O
N
SePh
SPh
210 (21%)
Ph3SnH
AIBN
H
O
N
H
SPh
211a (39%)
O
N
SPh
211b (51%)

eq. 78

The yield of this reaction was not optimized, since the in 51% yield. Nonetheless, a 39% yield of the desired quinolizidine **211a** was obtained. We assigned the *syn* stereochemistry to the bridgehead hydrogen and the $PhSCH_2$ group, again, based on the absence of strong Bohlmann bands. This stereochemistry was supported* by the reduction of sulfide **211a** with Raney nickel, to produce **212** (eq. 79). This compound is a naturally occurring quinolizidine alkaloid,[76a] that is differentiable (^1H NMR, IR) from the C(4) epimer.[76]



212

eq. 79

With these results in hand, we turned our attention to the possible synthesis of a naturally occurring indolizidine. The indolizidine alkaloids include a large number of compounds, and the gross structures of some of the simple members can be readily assembled via the Diels-Alder/radical cyclization methodology. A few such examples are shown in Fig. 7. These include a number of the *dendrobates* alkaloids, such as **213**, which is an alkaloid isolated from the skin of certain South American frogs.[77] The compounds are of considerable interest due to their effects on the nervous system. An isomer of the *dendrobates* alkaloid is compound **214**, monomorine I, a pheromone of the Pharoah ant (*Monomorium pharaonis L.*) which is a pest found in hospitals in Europe.[78] The 3-furyl substituted indolizidine **215**, a Nuphar alkaloid, is a minor component (<0.002%) of *castoreum* which is the extract from the dried scent glands of the Canadian Beaver (*Castor fiber L.*).[79] This extract has commercial value in perfumery. The gross structure of **215** was determined by mass spectroscopy[79a] but the stereochemistry has never been established.

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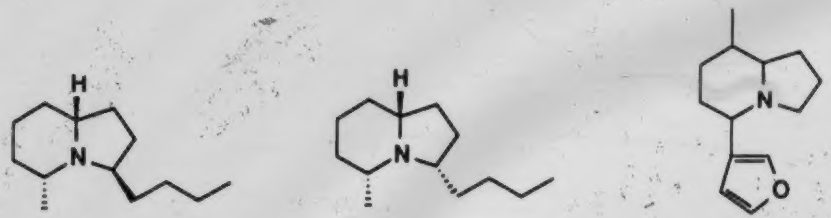
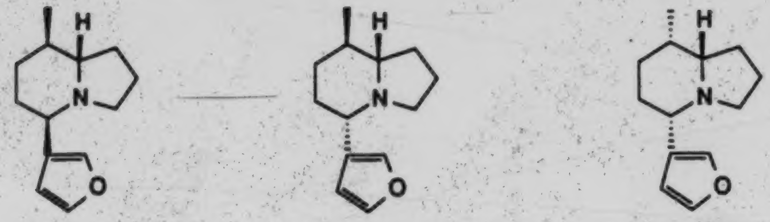
*This is not an absolute confirmation since isomerization is possible during the Raney nickel reduction.



213 **214** **215**

Fig. 7 Indolizidine alkaloids

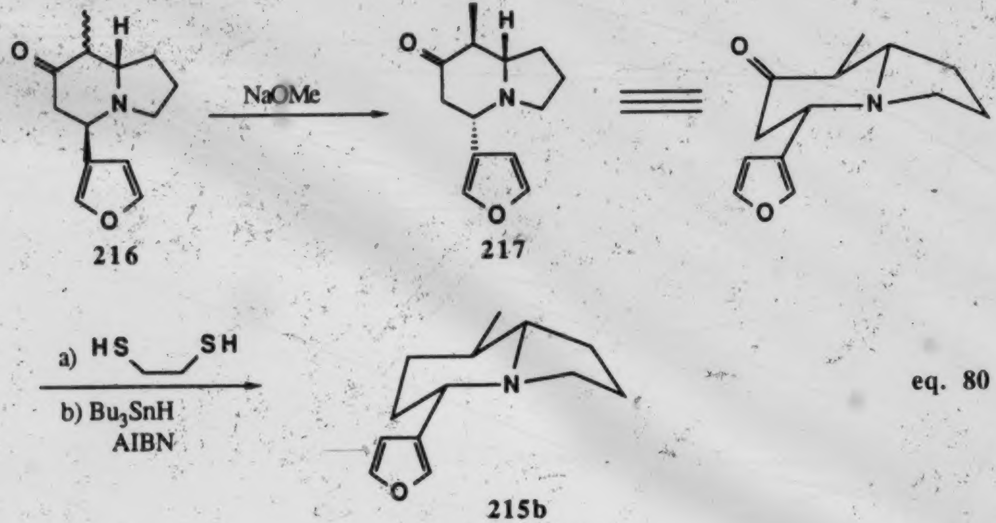
The Nuphar alkaloid **215** was chosen as the first target. Of the four possible isomers corresponding to the gross structure of the natural product, three have been synthesized in racemic form.[79b-d] These have the stereochemistries shown in Fig. 8.



215a **215b** **215c**

Fig. 8 Known stereoisomers of alkaloid **215**

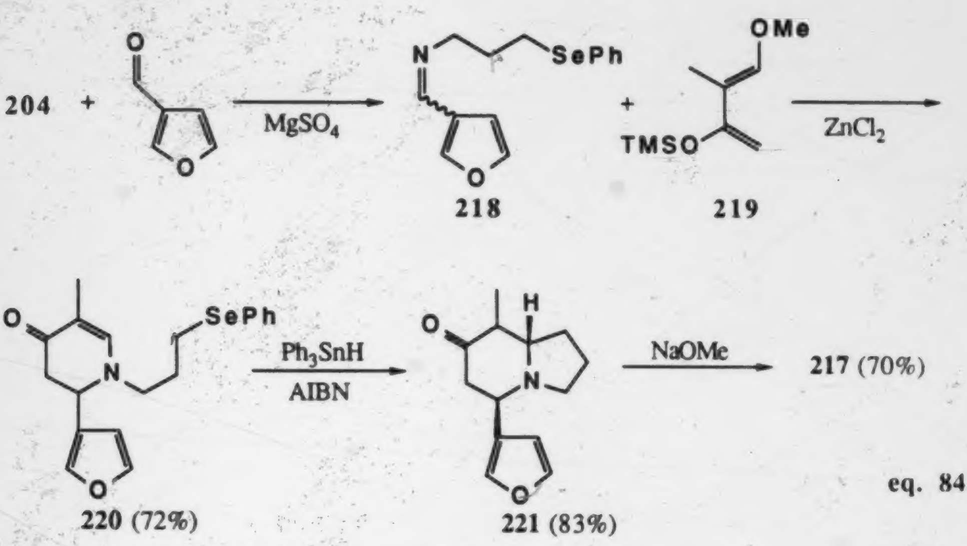
Of interest to us was that isomer **215b**, with the the all equatorial conformation, was made from the bicyclic ketone **216**, by base-catalyzed equilibration and removal of the carbonyl (eq. 80).[79b]



216 **217** **215b**

eq. 80

The gross structure of compound **216** is available by the Diels-Alder/radical cyclization technology using diene **218**[80] (eq. 81). The required imine **219** was assembled using the same method as before, by mixing the selenoamine **204** with commercial 3-furaldehyde in the presence of anhydrous magnesium sulfate. The crude imine was then treated with an excess of diene **218**, in the presence of anhydrous zinc chloride. After a reaction period of 48 hours, the cyclic adduct **220** was isolated. Treatment with triphenyltin hydride induced efficient ring closure to give **221**.



eq. 84

Compound **221** was a single isomer with the indicated *syn* stereochemistry of the furyl group and the bridgehead hydrogen. This assignment was based on the IR spectrum, (weak Bohlmann bands) and it is consistent with our previous results (**207a**). The relative stereochemistry of the methyl group has not been unambiguously assigned, although nOe experiments are consistent with the configuration shown in Fig. 9. Irradiation of the methyl group showed only the two indicated enhancements and *no* enhancements across the ring, suggesting that the methyl group is equatorial. The axial hydrogen *alpha* to the methyl group could not be selectively irradiated. The hydrogen *alpha* to the furyl group was also irradiated, but this experiment did not unambiguously support the assigned structure since similar enhancements could be expected if it was in an equatorial position. However, compound **221** is crystalline and has been submitted for X-ray analysis.

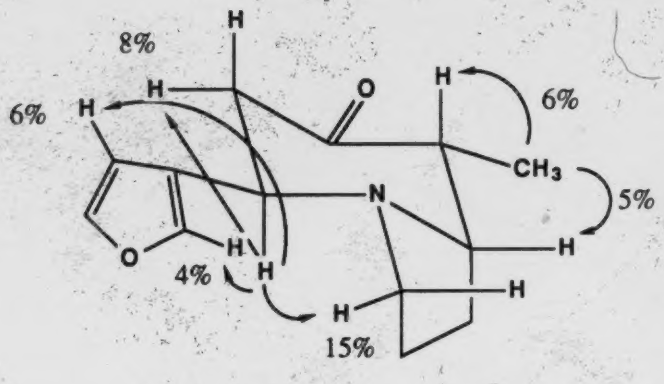
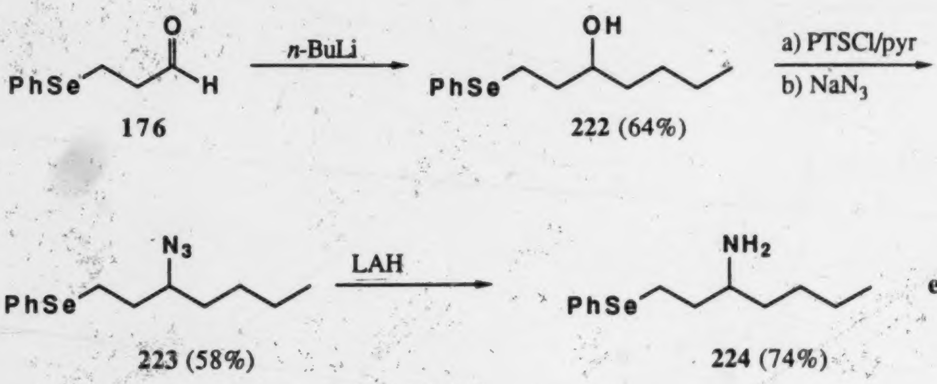


Fig. 9 nOe of **221**

Ketone **221** was equilibratable via the known procedure, producing **217**, the literature compound that had been converted to the all equatorial **215b**.[79b] No sample of the natural material is available and so the stereochemistry of the natural compound remains unknown.

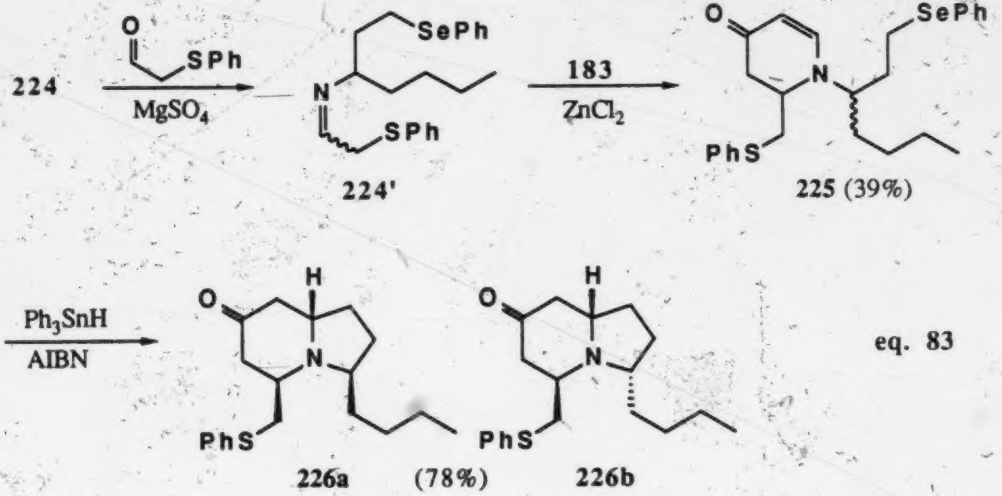
We then turned our attention towards the synthesis of **213** and/or **214**. All four possible isomers of the general structure of these two alkaloids have been synthesized (in that corresponded to the stereochemistry of the natural products **213** and **214** both exhibited Bohlmann bands. Although one could not predict the stereochemistry of the products of the radical cyclization step, we were encouraged by the additional possibility of isomerization, analogous to the conversion of **221** to **217** and the spontaneous isomerization of **207a** to **207b**. We decided, therefore, to try to determine experimentally the stereochemical outcome of the radical closure and the subsequent isomerization.

For our proposed synthesis of these alkaloids, amine **224** was required, and it was constructed by the addition of *n*-butyllithium to aldehyde **176** (eq. 82). Conversion of the resulting alcohol **222** to amine **224** was effected via tosylation, displacement with azide, followed by lithium aluminum hydride reduction.



eq. 82

The methyl group present in these indolizidine alkaloids was incorporated via imine formation with an acetaldehyde equivalent. (Phenylthio)acetaldehyde was suitable in this regard, since the phenylthio group could easily be removed at a later stage. Cycloaddition with diene **183** produced the desired adducts **225** as a mixture of diastereomers, and radical closure occurred without incident to give an inseparable mixture of the two stereoisomers, **226a** and **226b** (eq. 83). Neither isomer exhibited strong Bohlmann bands.


224
O
SPh
MgSO4
SePh
N
SPh
224'
183
ZnCl2
O
SePh
N
PhS
225 (39%)
Ph3SnH
AIBN
H
O
N
PhS
226a
(78%)
H
O
N
PhS
226b

eq. 83

It light of the fact that radical attack occurs preferentially from an axial direction (see Scheme 22), and due to the absence of strong Bohlmann bands, the stereochemistry has been tentatively assigned as shown in eq. 83. Using the procedure that was successful in isomerizing **221**, a small amount of a new isomer **226c** was obtained, that *did* show medium intensity Bohlmann bands. Compound **226c** has been tentatively assigned the structure shown in Fig. 10, which has two hydrogens antiperiplanar the nitrogen lone pair. This stereochemistry corresponds to the natural product **213** which is known to exhibit medium strength Bohlmann bands.[78b]

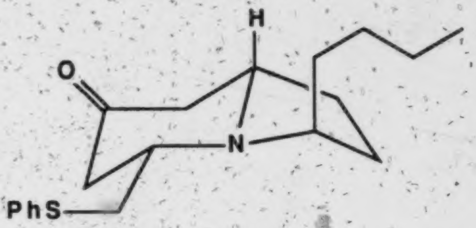
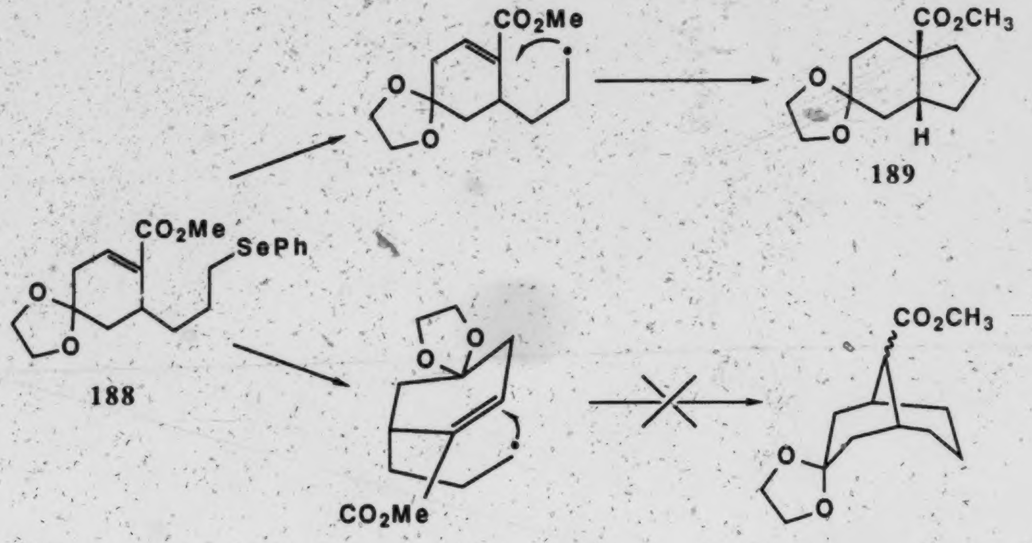


Fig. 10 Configuration of **226c**

Unfortunately, attempts to optimize this conversion to a useful level were not successful. Diastereomers **226a** and **226b** can be separated chromatographically after conversion to the corresponding thioketals (see Experimental, compounds **227a** and **227b**). Further work is underway to fully characterize the stereochemistry of these compounds.

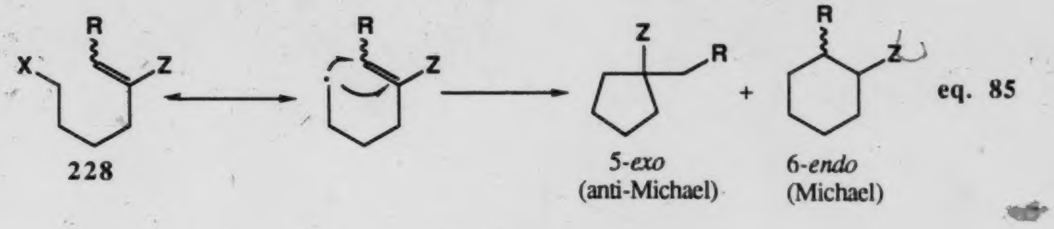
5-*Exo* vs 6-*Endo* Michael Cyclizations

In our efforts to construct a bridged carbocycle via 6-*endo* Michael radical cyclization of **188**, we observed exclusively the formation of a five-membered ring via 5-*exo* ring closure in an anti-Michael fashion (eq. 84).



eq. 84

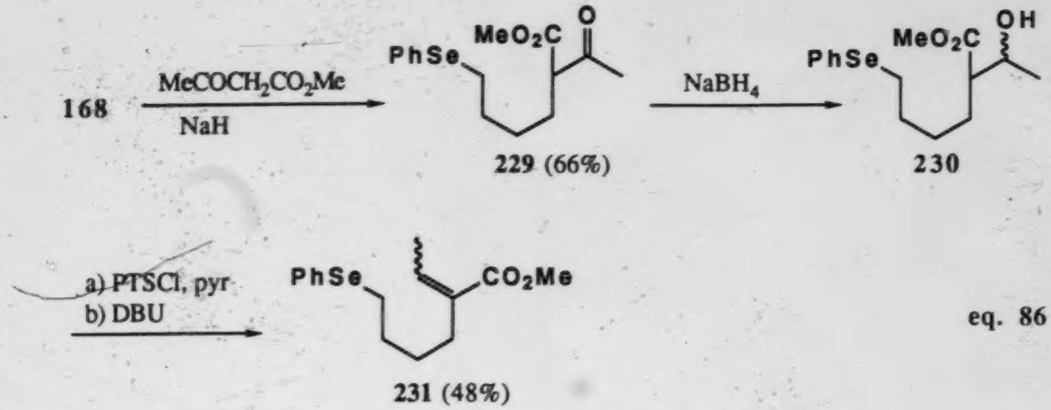
This result is in agreement with the general observation that the major product of a radical closure arises from the transition state in which the radical can best approach the LUMO of the olefin.[5] However, it is also well accepted that electron-withrawing groups on the olefin activate the *beta* position for radical addition by lowering the energy level of the LUMO, and thereby causing better overlap of the LUMO of the olefin with the SOMO of the radical.[81] In light of this, we have examined the circumstances under which the SOMO-LUMO overlap that favours 6-*endo* Michael closure can override the stereoelectronic effects that favour 5-*exo* closure. The system chosen for the study was the radical cyclization of compounds of general structure **228** (eq. 85) where R equals hydrogen or methyl, and electron withdrawing group Z is an ester, nitrile, or sulfone.



eq. 85

The desired model compounds were readily synthesized by a variety of techniques starting from bromo selenide **168**. Methyl ester **170** was in hand from previous work (eq. 62). Methyl substituted ester **231** was made by alkylation of methyl acetoacetate with **168** to give keto ester **229** (eq. 86).

Selective reduction of the ketone produced alcohol **230** and elimination via the corresponding tosylate provided **231**. The product was a mixture of geometrical isomers. In this and related cases, the rates of closure for the *Z* and *E* isomers are not the same[5] but the ratios of *exo* to *endo* ring closure for each isomer are expected to be comparable.[5]


168
MeCOCH₂CO₂Me
NaH
PhSe
MeO₂C
O
NaBH₄
PhSe
MeO₂C
OH
a) PTSCl, pyr
b) DBU
PhSe
CO₂Me

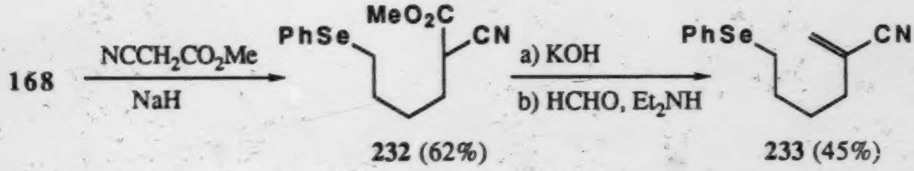
229 (66%)

230

231 (48%)

eq. 86

The same approach used for the synthesis of **170** provided nitrile **233**. Alkylation of methyl cyanoacetate with bromide **168** gave cyanoester **232**. Hydrolysis of the ester, followed by decarboxylation, and Mannich reaction with formaldehyde, furnished **233** (eq. 87).

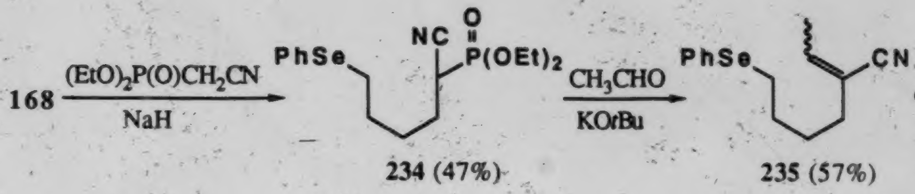

168
NCCH₂CO₂Me
NaH
PhSe
MeO₂C
CN
a) KOH
b) HCHO, Et₂NH
PhSe
CN

232 (62%)

233 (45%)

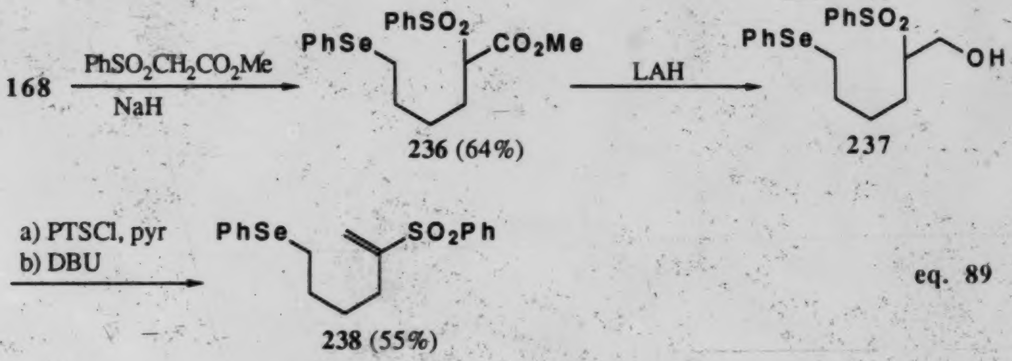
eq. 87

Methyl substituted nitrile **235** was synthesized by alkylation of commercially available (dimethylphosphono)-acetonitrile with **168** to give the phosphonate **234**. Horner-Emmons reaction with acetaldehyde provided **235** (eq. 88).


168
(EtO)$_2$P(O)CH$_2$CN
NaH
PhSe
NC
O
P(OEt)$_2$
234 (47%)
CH$_3$CHO
KOtBu
PhSe
CN
235 (57%)

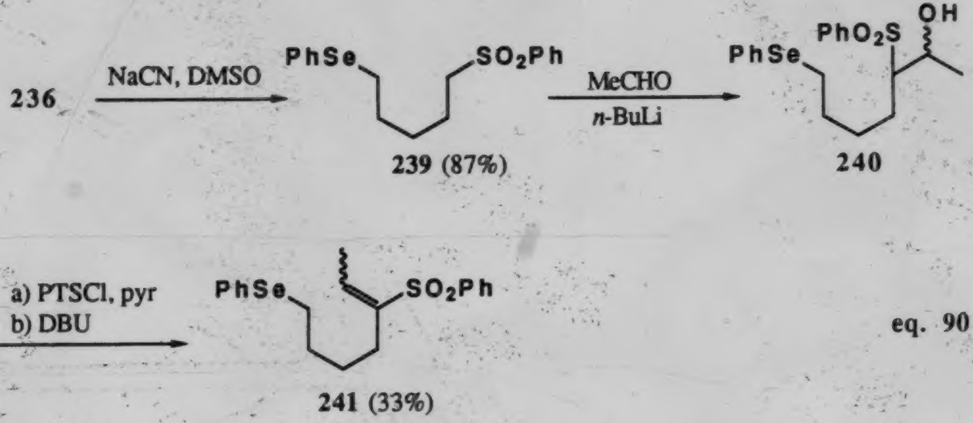
eq. 88

Sulfone **238** was prepared along the same lines as ester **231**. Alkylation of methyl (phenylsulfonyl)acetate gave the adduct **236**. Reduction of the ester with lithium aluminum hydride followed by elimination as before, provided sulfone **238** (eq. 89).


168
PhSO$_2$CH$_2$CO$_2$Me
NaH
PhSe
PhSO$_2$
CO$_2$Me
236 (64%)
LAH
PhSe
PhSO$_2$
OH
237
a) PTSCl, pyr
b) DBU
PhSe
SO$_2$Ph
238 (55%)

eq. 89

The methyl substituted sulfone **241** was constructed from **236** by a decarboxylation reaction to give phenylseleno sulfone **239**. Condensation with acetaldehyde resulted in alcohol **240** and elimination via the corresponding tosylate provided **241** (eq. 90).



eq. 90

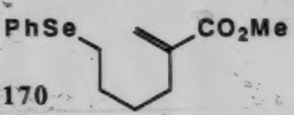
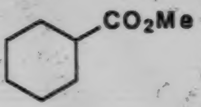
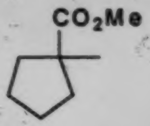
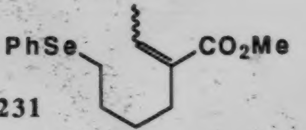
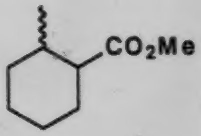
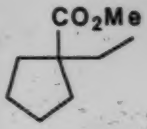
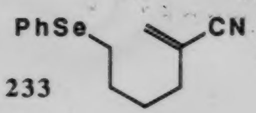
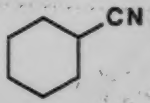
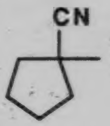
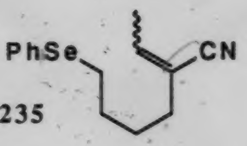
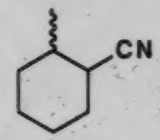
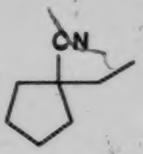
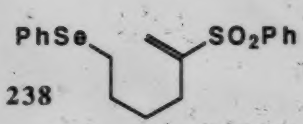
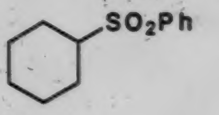
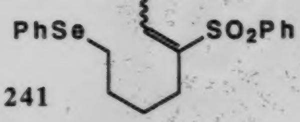
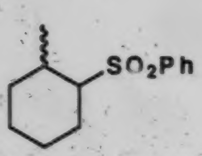
It should be noted that there are several potential routes for the synthesis of these compounds, and those used at the time were chosen on the basis of convenience. The yields for the reactions of equations 85 to 90 are satisfactory, but have not been optimized.

The results of the radical ring closure of these olefins are shown in Table 4. The ratio of the products was determined by ^1H NMR and/or g.c. analysis.

For all values of Z, and R = H (see **228**), the cyclization showed a strong preference for the 6-*endo* mode. For Z = sulfone (**238**), 6-*endo* Michael addition was observed exclusively. These results are in line with two examples that have recently appeared in the literature.[17a,b] However, in the case of **231** (Z = ester, R = methyl), a 3:1 ratio in favour of the 5-*exo* anti-Michael adduct was obtained. It is clear that the electron withdrawing ability of the ester function is not sufficiently large to overcome the steric effect of the methyl group.

TABLE 4

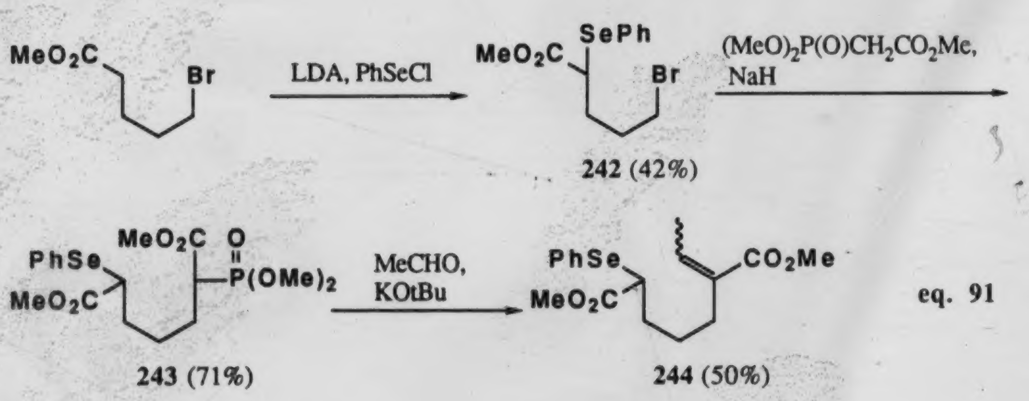
6-*Endo* Michael *vs* 5-*exo* Anti-Michael Ring Closure

Starting olefin	cyclized products		ratio (*endo*:*exo*)	combined yield
 170			7 : 1	93%
 231			1 : 3	90%
 233			>20 : 1	90%
 235			2.6 : 1	77%[a]
 238		_b	–	84%
 241		_b	–	51%[c]

(a) ~10% reduction product was detected. (b) No 5-*exo* product was detected. (c) ~16% reduction product detected.

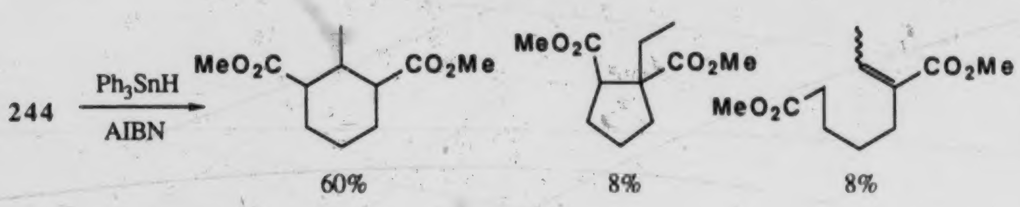
However, the ratio of the products for Z = nitrile, (**235**), was 2.6:1 ratio favouring 6-*endo* Michael closure. In addition, in both cases where Z = sulfone (**238** and **241**), no 5-*exo* product was detected. The results shown in Table 4 clearly show that the use of a strong electron withdrawer can induce 6-*endo* radical closure.

Another consideration regarding the induction of 6-*endo* closure is the stability of the radical. The idea here is that a more stable radical may be more selective, and therefore favour the thermodynamic product, i.e., the six-membered ring. The obvious choice for this experiment is **244** (eq. 91), since the radical closure of **231** gave a mixture of products (see Table 4). Compound **244** was constructed along the lines used for compound **235**, from methyl 5-bromo-2-(phenylseleno)pentanoate **242** (eq. 91).


MeO2C
Br
LDA, PhSeCl
MeO2C
SePh
Br
(MeO)2P(O)CH2CO2Me, NaH
242 (42%)
PhSe
MeO2C
MeO2C
O
P(OMe)2
MeCHO, KOtBu
PhSe
MeO2C
CO2Me
243 (71%)
244 (50%)

eq. 91

Alkylation of trimethyl phosphonoacetate with bromide **242** afforded phosphonate **243**. Horner-Emmons reaction with acetaldehyde provided the desired α-seleno ester **244** as a mixture of isomers. Radical cyclization of **244** produced a 76% yield of a mixture of products of which the major component was determined (^{1}H NMR, g.c. analysis) to be the 6-*endo* product (eq. 93).



eq. 92

It is not clear if the presence of a more stabilized radical causes a better energy level overlap between the SOMO of the radical and the LUMO of the olefin and it is also not known what role is played, in the result of eq. 92, by the fact that the radical is in the same plane as the p orbitals of the pi bonds of the carbonyl.[13b] Neither of the ring closures of **244** is overly efficient, since reduction product was obtained, but in contrast to the case of **231**, formation of a six-membered ring is now favoured.

There remains another important factor with regard to the regiochemistry of radical ring closure. This is the case of cyclization when the pendants are attached to a ring.[8,11c] Work is currently underway in this laboratory to examine the regiochemical outcome of this type of reaction.

III. CONCLUSION

The results described in this manuscript indicate that the Diels-Alder/radical cyclization sequence is a highly versatile methodology, that can be applied to the synthesis of a wide range of polycyclic compounds, including *cis*-fused 6-5 systems, bridged structures, spiro compounds, as well as both oxygen- and nitrogen- containing heterocycles.

It is also been shown that by judicious use of electron withdrawing groups, the rarely encountered 6-*endo* mode of cyclization can be preferred over the more common 5-*exo* process.

IV. EXPERIMENTAL

Unless otherwise stated, the following general experimental techniques were followed.

Experiments that required an inert atmosphere were conducted under argon that was purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[82] and then through an identical column of Drierite. Glassware was dried in an oven at 120°C for at least 3 h, cooled in a desiccator, fitted with a rubber septum and flushed, via needles, with argon. The exit needle was removed, and materials were added to the flask as solutions, using dry syringes, or by quick transfer using a pipette or spatula. Reactions were carried out under a static pressure of argon, and stirring was effected using a Teflon-coated magnetic stirring bar.

Solvents were distilled immediately prior to use. Where required, solvents and reagents were distilled from suitable drying agents, under argon. Ether, THF, and dioxane were distilled from sodium-benzophenone ketyl; benzene, toluene, and xylene were distilled from sodium; dichloromethane, chloroform, carbon tetrachloride, triethylamine, diisopropylamine, dimethylsulfoxide were distilled from calcium hydride, the latter at 14 mm Hg. U.S.P absolute ethanol was used without further purification. All other commercial reagents were used as received.

Evaporation of solvents was done on a rotary evaporator at water pump vacuum (~14 mm Hg) and at a bath temperature of about 35°C.

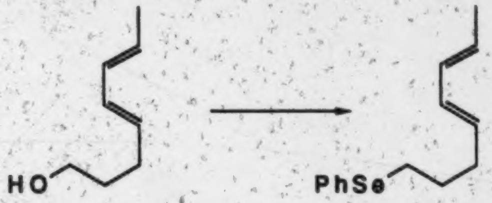
Commercial silica (Merck 60F-254) thin-layer chromatography (tlc) plates were used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). The developed tlc plates were examined under UV radiation (254 nm), and then charred after being dipped in a solution of phosphomolybdic acid[83] or sprayed with an acidic solution of anisaldehyde in 95% ethanol.[84]

All spectra were obtained at the laboratories at the University of Alberta. Melting points were measured with a Kofler block melting point apparatus. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature. Infrared spectra were recorded on a Nicolet 7000 FT-IR spectrometer. Liquids were run as neat films on potassium chloride plates, and solids were run as solutions in chloroform in 0.5 mm potassium chloride cells. Proton NMR spectra were recorded on Bruker WP-80 (80 MHz), Bruker WH-200 (200 MHz), Bruker WH-300 (300 MHz), or Bruker WH-400 (400 MHz) spectrometers in deuterated chloroform using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on the Bruker WH-300 (300 MHz) or the Bruker WH-400 (400 MHz) spectrometers at 75.5 and 100.6 MHz, respectively. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant; δ, chemical shift. Mass spectra were recorded on a A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 eV. Gas chromatography (g.c.) was done on a Hewlett Packard 5830A gas chromatograph.

All compounds with asymmetric centers are racemic. In some cases where a mixture of isomers was obtained, not all signals in the ^{13}C NMR were observed, and the ratios given were deduced from ^{1}H NMR or g.c. analysis where indicated.

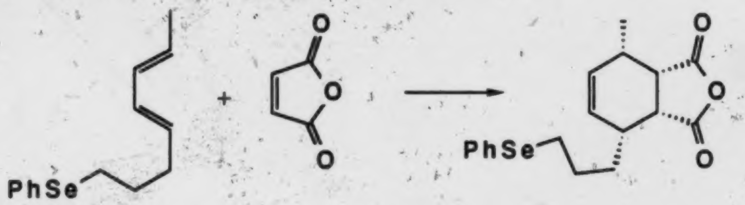
General Procedure for Radical Cyclization. The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with argon for 5-10 min, and sufficient dry benzene was injected to give an approximately 0.02-0.008 M solution. The flask was lowered into an oil bath preheated to 90°C, and dry benzene solutions of triphenyltin hydride (1.5 equiv, *ca* 0.02 M) and AIBN (0.3 equiv, *ca* 0.006 M) were injected simultaneously with a double syringe pump set at a rate of 1 mL/h. Refluxing was continued for an arbitrary period of 2 h after the end of the addition. The reaction mixture was cooled and evaporation of the solvent gave a residue that was processed as described for the individual examples.

(*E*,*E*)-1-(Phenylseleno)octa-4,6-diene (143).



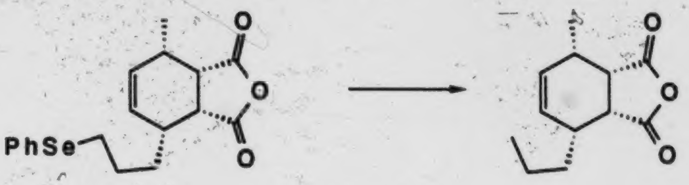
A general literature procedure[52] was followed. Tributylphosphine (0.15 mL, 122 mg, 0.602 mmol) in dry THF (3.0 mL) was added to a stirred solution of (*E*,*E*)-octa-4,6-dienol (**142**)[51] (65 mg, 0.516 mmol) and phenylselenocyanate (114 mg, 0.619 mmol) in THF (2.0 mL). The solution was stirred for 30 min and was then evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:99 ethyl acetate-hexane gave **143** (87 mg, 64%) as an oil containing about 10% of a stereoisomer (^{1}H NMR, 200 MHz). Compound **143** had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.72 (d, J = 6.0 Hz, 3 H), 1.79 (q, J = 7.3 Hz, 2 H), 2.17 (q, J = 7.2 Hz, 2 H), 2.9 (t, J = 7.3 Hz, 2 H), 5.35-5.65 (m, 2 H), 5.91-6.06 (m, 2 H), 7.18-7.30 (m, 3 H), 7.43-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.03, 27.32, 29.81, 32.51, 126.71, 127.39, 129.01, 130.29, 130.46, 131.31, 131.48, 132.57; exact mass, *m/z* calcd for $C_{14}H_{18}Se$ 266.0574, found 266.0571. Anal. Calcd for $C_{14}H_{18}Se$: C, 63.39; H, 6.84. Found: C, 63.54; H, 6.71.

(1α,2α,3α,6α)-6-Methyl-3-[3-(phenylseleno)propyl]-4-cyclohexene-1,2-dicarboxylic anhydride (144).



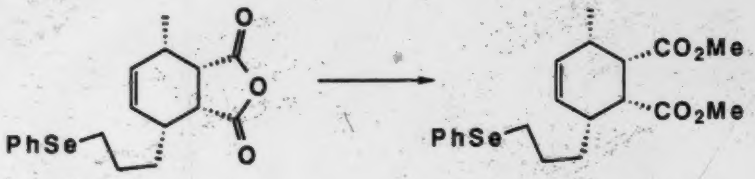
Diene **143** (200 mg, 0.754 mmol) and maleic anhydride (75.0 mg, 0.765 mmol) were dissolved in anhydrous benzene (5 mL) and the solution was refluxed for 6 h under argon. Evaporation of the solvent and crystallization of the residue from ethyl acetate-hexane gave **144** (159 mg). Evaporation of the mother liquor and flash chromatography of the residue over silica gel (1 x 15 cm) with 1:3 ethyl acetate-hexane gave a further crop of **144** (46 mg) as a white, homogeneous (^{1}H NMR, 200 MHz) solid. The total yield of **144** amounted to 205 mg (75%): mp 103°C; FT-IR ($CHCl_3$ cast) 1772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (d, J = 7.2 Hz, 3 H), 1.74-2.08 (m, 4 H), 2.22 (td, J = 7.0, 5.9 Hz, 1 H), 2.42 (qd, J = 6.5, 7.2 Hz, 1 H), 2.89-3.04 (m, 2 H), 3.24 (dd, J = 6.5, 9.4 Hz, 1 H), 3.31 (dd, J = 5.9, 9.4 Hz, 1 H), 5.76 (d, J = 11 Hz, 1 H), 5.78 (d, J = 11 Hz, 1 H), 7.22-7.31 (m, 3 H), 7.47-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.37, 27.38, 28.55, 30.65, 30.84, 35.68, 45.03, 46.25, 126.90, 129.13, 130.25, 132.63, 133.19, 134.97, 171.28, 171.39; exact mass, *m/z* calcd for $C_{18}H_{20}O_3Se$ 364.0578, found 364.0600. Anal. Calcd for $C_{18}H_{20}O_3Se$: C, 59.51; H, 5.55;. Found: C, 59.57; H, 5.68.

(1α,2α,3α,6α)-6-Methyl-3-propyl-4-cyclohexene-1,2-dicarboxylic anhydride (145).



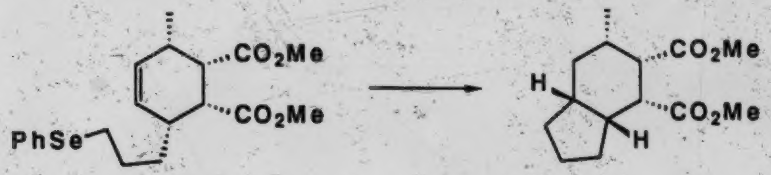
The general procedure for radical cyclization was followed using selenide **144** (32 mg, 0.088 mmol) in benzene (20 mL), triphenyltin hydride (40 μL, 55 mg, 0.157 mmol) in benzene (5 mL), and AIBN (3 mg, 0.018 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave an oil (15 mg, 83%) consisting of a mixture (^{1}H NMR, 200 MHz)) of two compounds. Kugelrohr distillation [70°C (0.3 mm Hg)] gave pure **145** (11 mg, 60%) as a white solid: mp 56°C; FT-IR ($CHCl_3$ cast) 1740, 1845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (t, J = 7.0 Hz, 3 H), 1.40-1.60 (m, 2 H), 1.53 (d, J = 7.4 Hz, 3 H), 1.75-2.05 (m, 2 H), 2.25 (m, 1 H), 2.45 (m, 1 H), 3.28-3.47 (m, 2 H), 5.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.01, 16.39, 21.12, 30.65, 32.86, 35.93, 45.14, 46.38, 133.76, 134.63, 171.52; exact mass, *m/z* calcd for $C_{12}H_{16}O_3$ 208.1100, found 208.1101. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.10; H, 7.59.

Dimethyl (1α,2α,3α,6α)-6-Methyl-3-[3-(phenylseleno)propyl]-4-cyclohexene-1,2-dicarboxylate (146).



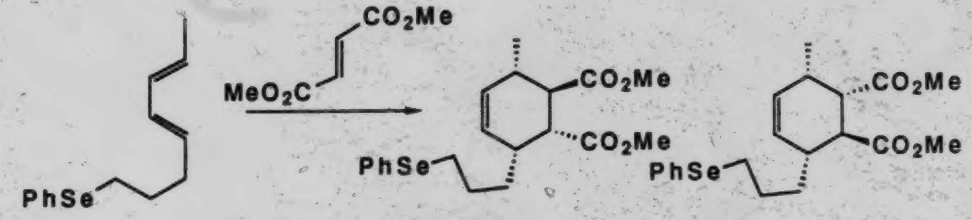
Diels-Alder adduct **144** (113 mg, 0.311 mmol) was heated for 14 h in refluxing methanol (5 mL) containing concentrated sulfuric acid (5 µL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave **146** (113 mg, 89%) as a clear, homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.08 (d, J = 7.5 Hz, 3 H), 1.45-1.68 (m, 2 H), 1.71-1.91 (m, 2 H), 2.34-2.44 (m, 1 H), 2.60-2.72 (m, 1 H), 2.89 (t, J = 7.4 Hz, 2 H), 3.08 (dd, J = 6.2, 4.3 Hz, 1 H), 3.03 (dd, J = 7.2, 4.3 Hz, 1 H), 3.65 (s, 3 H), 3.71 (s, 3 H), 5.56 (ddd, J = 10.0, 2.0, 1.5 Hz, 1 H), 5.63 (ddd, J = 10.0, 2.5, 2.0 Hz, 1 H), 7.19-7.30 (m, 3 H), 7.46-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.94, 27.73, 28.51, 30.96, 32.57, 36.84, 43.13, 45.13, 51.31, 51.43, 126.73, 127.26, 129.05, 130.58, 131.13, 132.49, 173.09, 173.33; exact mass, *m/z* calcd for $C_{20}H_{26}O_4Se$ 410.0996, found 410.1005. Anal. Calcd for $C_{20}H_{26}O_4Se$: C,58.68; H, 6.40; O, 15.63. Found: C, 58.80; H, 6.55; O, 15.75.

Dimethyl (3aβ,4α,5α,6α,7aβ)-6-Methyloctahydro-1*H*-indene-4,5-dicarboxylate (147).



The general procedure for radical cyclization was followed using selenide **146** (80 mg, 0.195 mmol) in benzene (20 mL), triphenyltin hydride (75 μL, 103 mg, 0.294 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane followed by Kugelrohr distillation gave **147** (40 mg, 80%) as a white, homogeneous (^{1}H NMR) solid: mp 32°C, FT-IR (CHCl$_3$ cast) 1736 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.00 (d, J = 4.9 Hz, 3 H), 1.16-1.25 (m, 1 H), 1.34-1.81 (m, 7 H), 1.90-2.03 (m, 2 H), 2.26-2.37 (m, 1 H), 2.94 (dd, J = 4.8 Hz, 1 H), 2.98 (dd, J = 5.7 Hz, 1 H), 3.65 (s, 3 H), 3.68 (s, 3 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 19.69, 22.65, 24.85, 31.35, 31.97, 33.93, 39.43, 40.16, 45.03, 45.96, 51.10, 51.62, 173.94, 174.21; exact mass, *m/z* calcd for C$_{14}$H$_{22}$O$_4$ 254.1518, found 254.1522. Anal. Calcd for C$_{14}$H$_{22}$O$_4$: C, 66.12; H, 8.72. Found: C, 66.36; H, 8.67.

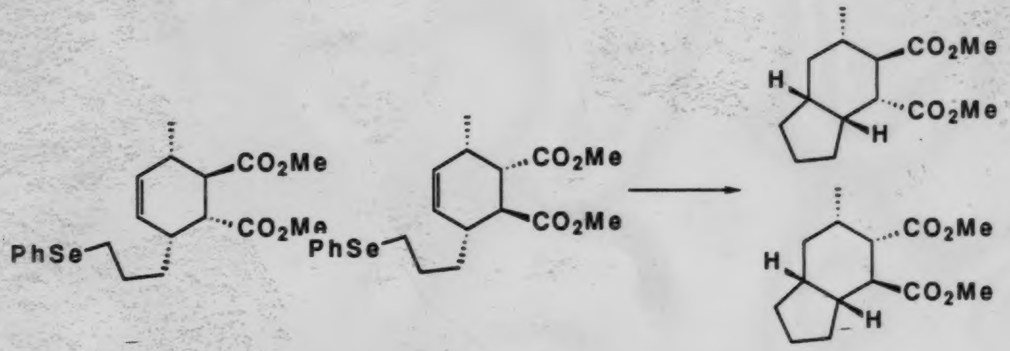
Dimethyl (1α,2β,3β,6β)-6-Methyl-3-[3-(phenylseleno)propyl]-4-cyclohexene-1,2-dicarboxylate (148a) and Dimethyl (1α,2β,3α,6α)-6-Methyl-3-[3-(phenylseleno)propyl]-4-cyclohexene-1,2-dicarboxylate (148b).



Diene **143** (49 mg, 0.185 mmol) and dimethyl fumarate (40 mg, 0.278 mmol) were dissolved in dry xylene (3 mL) and the solution was refluxed for 36 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15) with 1:9 ethyl acetate-hexane gave **148a** and **148b** (54 mg, 71%) as a 1:1 mixture (^{1}H NMR, 200 MHz) that was inseparable by chromatography: FT-IR (CHCl$_3$ cast) 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.83 (d, J = 7.0 Hz, 1.5 H), 1.03 (d, J = 7.0 Hz, 1.5 H), 1.22-1.35 (m, 1 H), 1.36-1.38 (m, 0.5 H), 1.54-1.69 (m, 1.5 H), 1.71-1.91 (m, 1 H), 2.26-2.38 (m, 1 H), 2.43 (dd, J = 11.6, 10.5 Hz, 0.5 H), 2.48-2.60 (m, 0.5 H), 2.55 (dd, J = 11.0, 12.0 Hz, 0.5 H), 2.61-2.73 (m, 0.5 H), 2.78-2.92 (m, 2 H), 3.05 (dd, J = 5.5, 6.6 Hz, 0.5 H), 3.10 (dd, J = 5.5, 6.5 Hz, 0.5 H), 3.66 (s, 1.5 H), 3.68 (s, 1.5 H), 3.71 (s, 1.5 H), 3.72 (s, 1.5 H), 5.45 (ddd, J = 5.4, 1.4, 1.4 Hz, 0.5 H), 5.48 (ddd, J = 5.5, 1.5, 1.5 Hz, 0.5 H), 5.68 (ddd, J = 5.1, 5.1, 1.6 Hz, 0.5 H), 5.70 (ddd, J = 5.1, 5.1, 2.5 Hz, 0.5 H), 7.2-7.28 (m, 3 H), 7.44-7.50 (m, 2 H);

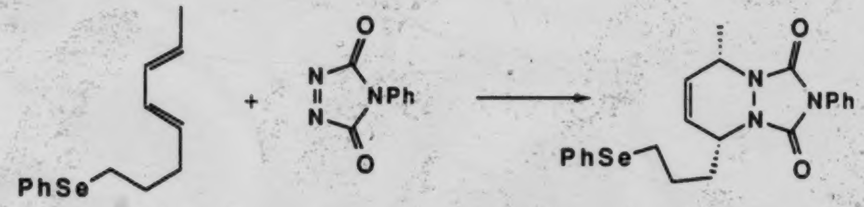
^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 16.82, 19.81, 25.89, 27.70, 27.74, 28.01, 31.13, 32.70, 32.93, 34.94, 35.47, 39.22, 41.79, 45.14, 46.55, 46.59, 51.69, 51.74, 126.75, 126.84, 127.94, 128.15, 129.02, 130.20, 130.41, 131.45, 131.82, 132.54, 132.73, 173.97, 176.08; exact mass, *m/z* calcd for $C_{20}H_{26}O_4Se$ 410.0996, found 410.1001. Anal. Calcd for $C_{20}H_{26}O_4Se$: C, 58.68; H, 6.40; O, 15.63. Found: C, 58.57; H, 6.39; O, 15.49.

Dimethyl (3aβ,4α,5β,6α,7aβ)-6-Methyloctahydro-1*H*-indene-4,5-dicarboxylate (149a) and Dimethyl (3aα,4α,5β,6β,7aα)-6-Methyloctahydro-1*H*-indene-4,5-dicarboxylate (149b).



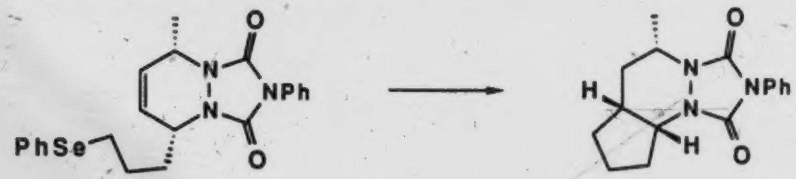
The general procedure for radical cyclization was followed using selenides **148a** and **148b** (62 mg, 0.225 mmol) in benzene (20 mL), triphenyltin hydride (86 µL, 118 mg, 0.337 mmol) in benzene (10 mL), and AIBN (10 mg, 0.037 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 7:93 ethyl acetate-hexane followed by Kugelrohr distillation [80°C (0.3 mm)] gave **149a** and **149b** (53 mg, 93%) as a 1:1 mixture (^{1}H NMR. 200 MHz) that was inseparable by chromatography: FT-IR (CHCl$_3$ cast) 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.81-0.94 (m, 0.5 H), 0.89 (d, J = 4.0 Hz, 1.5 H), 0.91 (d, J = 4.5 Hz, 1.5 H), 1.28-1.85 (m, 8 H), 1.97-2.12 (m, 1.5 H), 2.18-2.32 (m, 0.5 H), 2.36-2.47 (m, 0.5 H), 2.37 (t, J = 2.0 Hz, 0.5 H), 2.59 (t, J = 1.8 Hz, 0.5 H), 2.90 (dd, J = 11.4, 7.0 Hz, 0.5 H), 3.13 (dd, J = 11.4, 5.0 Hz, 0.5 H), 3.65 (s, 1.5 H), 3.66 (s, 1.5 H), 3.69 (s, 1.5 H), 3.70 (s, 1.5 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 18.60, 20.98, 22.21, 24.42, 24.94, 30.19, 31.46, 32.08, 32.77, 34.79, 35.60, 37.06, 38.24, 40.25, 41.46, 42.89, 43.76, 46.92, 47.68, 47.90, 52.30, 52.50, 175.33, 175.47, 177.10, 177.46; exact mass, *m/z* calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1507. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.35; H, 8.70.

(5α,8α)-5,8-Dihydro-8-methyl-2-phenyl-5-[3-(phenylseleno)propyl]-*s*-triazolo[1,2-*a*]pyridazine-1,3-dione (151).



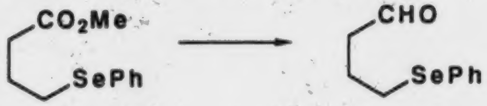
Diene **143** (32.3 mg, 0.122 mmol) in dry ether (1.5 mL) was added to the triazolinedione **150**^{53} (24.2 mg, 0.135 mmol) in dry ether (1.0 mL). The red color of the triazolinedione was discharged instantaneously, and evaporation of the solvent followed by flash chromatography of the residue over silica gel (1 x 15 cm) with 1:3 ethyl acetate-hexane gave **151** (43.3 mg, 81%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (d, J = 6.2 Hz, 3 H), 1.67-1.92 (m, 2 H), 1.95-2.07 (m, 1 H), 2.15-2.28 (m, 1 H), 2.87-3.00 (m, 2 H), 4.40-4.51 (m, 2 H), 5.73 (ddd, J = 10.0, 1.6, 0.6 Hz, 1 H), 5.81 (ddd, J = 10.0, 1.6, 0.7 Hz, 1 H), 7.24-7.34 (m, 3 H), 7.34-7.46 (m, 1 H), 7.46-7.62 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.18, 24.99, 27.50, 32.84, 50.70, 53.78, 124.38, 125.48, 127.00, 127.58, 128.01, 129.07, 129.88, 131.29, 132.96, 151.53, 152.10; exact mass, *m/z* calcd for $C_{22}H_{23}N_3O_2Se$ 441.0956, found 441.0958. Anal. Calcd for $C_{22}H_{23}N_3O_2Se$: C, 60.00; H, 5.26; N, 9.54; O, 7.27. Found: C, 60.04; H, 5.19; N, 9.44; O, 7.57.

(4α,5aβ,8aβ)-4-Methyldodecahydro-2-phenyl-2,3a,8b-triaza-*as*-indacene-1,3-dione (152).



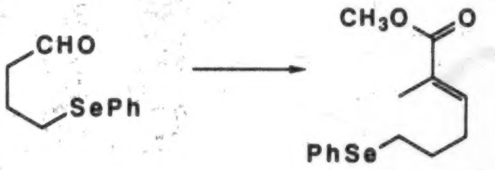
The general procedure for radical cyclization was followed using **151** (60 mg, 0.136 mmol) in benzene (25 mL), triphenyltin hydride (52 μL, 72 mg, 0.204 mmol) in benzene (10 mL), and AIBN (3 mg, 0.018 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:3 ethyl acetate-hexane gave **152** (30.7 mg, 79%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1765, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46-1.60 (m, 2 H), 1.66 (d, J = 6.3 Hz, 3 H), 1.67-1.97 (m, 5 H), 2.08-2.17 (m, 1 H), 2.24-2.33 (m, 1 H), 3.73 (sextet of d, J = 6.3, 3.8 Hz, 1 H), 4.36 (q, J = 7.7 Hz, 1 H), 7.32-7.36 (m, 1 H), 7.44-7.54 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.22, 21.24, 25.09, 29.10, 35.29, 35.49, 52.98, 52.06, 125.66, 127.88, 129.02, 131.52, 151.82, 152.86; exact mass, *m/z* calcd for $C_{16}H_{19}N_3O_2$ 285.1477, found 285.1477. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.27; H, 6.71; N, 14.63.

4-(Phenylseleno)butanal (154).



Diisobutylaluminum hydride (1.0 M in dichloromethane, 17.0 mL, 17.0 mmol) was added over 5 min to a stirred and cooled (-78°C) solution of methyl 4-(phenylseleno)butanoate[55] (**153**) (4.10 g, 15.94 mmol) in dry dichloromethane (30 mL). After 10 min, the reaction was quenched with water (30 mL) and the mixture was allowed to warm to room temperature over about 10 min. Dilute hydrochloric acid (2.0 M) was added to dissolve the precipitate and the mixture was then extracted with ether (3 x 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 1:9 ethyl acetate-hexane gave **154** (2.70 g, 75%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (quintet, J = 7.1 Hz, 2 H), 2.59 (td, J = 7.1, 1.0 Hz, 2 H), 2.92 (t, J = 7.1 Hz, 2 H), 7.23-7.28 (m, 3 H), 7.46-7.53 (m, 2 H), 9.74 (d, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.40, 26.94, 43.43, 126.95, 129.06, 129.58, 132.67, 210.37; exact mass, *m/z* calcd for $C_{10}H_{12}OSe$ 228.0054, found 280.0048. Anal. Calcd for $C_{10}H_{12}OSe$: C, 52.87; H, 5.33; O, 7.04. Found: C, 52.98; H, 5.33; O, 7.04.

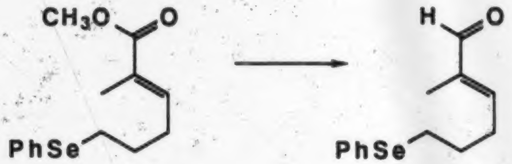
Methyl (*E*)-2-Methyl-6-(phenylseleno)-2-hexenoate (155).



A general literature procedure[56] was followed. Methyl α-(dimethylphosphono)propionate[57] (5.70 g, 29.06 mmol) was added to a stirred and cooled (0°C) solution of potassium *tert*-butoxide (3.26 g, 29.01 mmol) in THF (30 mL). The cooling bath was removed and stirring was continued for 30 min. The solution was recooled to -78°C and aldehyde **154** (6.05 g, 26.63 mmol) in THF (10 mL) was added over about 2 min. The cooling bath was removed after the addition and, after 10 min, the reaction was quenched by addition of water (30 mL). The mixture was extracted with ether (3 x 50 mL).

The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatograpy of the residue over silica gel (5 x 15 cm) with 1:25 ethyl acetate-hexane gave **155** (6.50 g, 83%) as a mixture of *Z* and *E* isomers (^1H NMR, 200 MHz). This material was isomerized by a general literature procedure.[56,58] Sodium 2-propanethiolate [from 2-propanethiol (400 mg, 5.252 mmol) and sodium hydride (60% w/w in oil, 63 mg, 1.575 mmol) in DMF (4.0 mL)] was added to a solution of the above isomers (3.5 g, 11.77 mmol) in DMF (50 mL) and the mixture was heated at 90°C for 30 min. The mixture was then cooled, quenched by addition of water (400 mL), and extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 1:25 ethyl acetate-hexane gave exclusively (^1H NMR, 200 MHz) the desired *E* isomer, **155** (3.01 g, 86%): FT-IR ($CHCl_3$ cast) 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.83 (d, J = 1.0 Hz, 3 H), 1.83 (quintet, J = 7.4 Hz, 2 H), 2.3 (q, J = 7.5 Hz, 2 H), 2.91 (t, J = 7.2 Hz, 2 H), 3.72 (s, 3 H), 6.71 (tq, J = 7.5, 1.0 Hz, 1 H), 7.22-7.30 (m, 3 H), 7.46-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.46, 27.31, 28.55, 28.84, 51.71, 126.89, 128.39, 129.05, 129.97, 132.71, 140.99, 168.00; exact mass, *m/z* calcd for $C_{14}H_{18}O_2Se$ 298.0472, found 298.0476. Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10; O, 10.80. Found: C, 56.66; H, 6.27; O, 10.47.

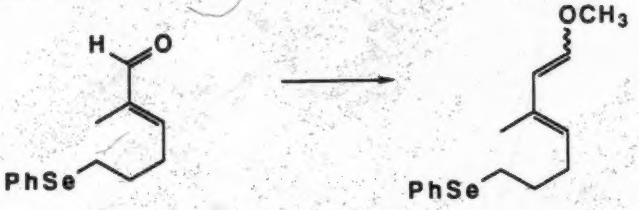
(*E*)-2-Methyl-6-(phenylseleno)-2-hexenal (156).



Ester **155** was reduced[59] according to the procedure followed with **153**, using **155** (3.673 g, 12.356 mmol) in dichloromethane (35 mL), and diisobutylaluminum hydride (1.0 M in dichloromethane, 25.0 mL, 25.0 mmol). The reaction was quenched with water (100 mL) and the mixture was extracted with ether (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give the corresponding alcohol, which was not isolated but was oxidized using a general literature procedure.[50a] The residue was taken up in dioxane (250 mL) and DDQ (2.98 g, 13.23 mmol) was added. The resulting mixture was refluxed for 3 h, cooled, filtered through a pad of grade 3 alumina (5 x 5 cm) with ether, and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 ethyl acetate-hexane gave **156** (1.71 g, 52% from **155**) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70 (s, 3 H), 1.88 (quintet, J = 5.8 Hz, 2 H), 2.47 (q, J = 5.6 Hz, 2 H), 2.94 (t, J = 7.3 Hz, 2 H), 6.44 (tq, J = 7.3, 1.2 Hz, 1 H), 7.23-7.31 (m, 3 H), 7.45-7.56 (m, 2 H), 9.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 9.31, 27.32, 28.76, 28.91, 127.11, 129.16, 129.53, 132.90, 140.10, 152.97, 195.06; exact mass, *m/z* calcd for $C_{13}H_{16}OSe$

268.0366, found 268.0366. Anal. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.04; O, 5.99. Found: C, 58.58; H, 6.20; O, 6.21.

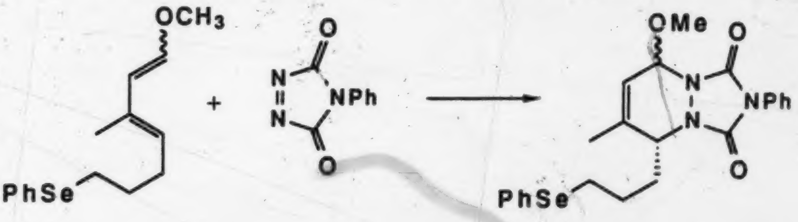
(1*Z*,6*E*)- and (1*E*,6*E*)-1-Methoxy-3-methyl-7-(phenylseleno)hepta-1,3-diene (157).



A general literature procedure[60] was followed. Potassium *tert*-butoxide (330 mg, 2.94 mmol) was added via a side-arm addition funnel to a suspension of (methoxymethyl)-triphenylphosphonium chloride (1.375 g, 3.998 mmol) in dioxane (10 mL) under argon. The mixture was stirred for 1.5 h and then a solution of **156** (311 mg, 1.163 mmol) in dioxane (2 mL) was added over about 2 min. Stirring at room temperature was continued for 20 h. The reaction was quenched by addition of water (5 mL) and the mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:50 ethyl acetate-hexane gave **157** (307 mg, 89%) as a 1:1 (^{1}H NMR, 300 MHz) mixture of isomers that were inseparable by chromatography: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 1.5 H), 1.70-1.84 (m, 2 H), 1.77 (s, 1.5 H), 2.22 (q, J = 7.3 Hz, 2 H), 2.90 (t, J = 7.5 Hz, 1 H), 2.91 (t, J = 7.3 Hz, 1 H), 3.57 (s, 1.5 H), 3.61 (s, 1.5 H), 5.05 (t, J =

7.3 Hz, 0.5 H), 5.22 (t, J = 7.3 Hz, 0.5 H), 5.56 (d, J = 12.7 Hz, 0.5 H), 5.85 (d, J = 13.0 Hz, 0.5 H), 6.5 (d, J = 12.7 Hz, 0.5 H), 6.58 (d, J = 13.0 Hz, 0.5 H), 7.17-7.22 (m, 3 H), 7.42-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.76, 20.66, 27.06, 27.46, 27.99, 30.15, 30.18, 56.42, 56.59, 103.46, 110.46, 124.78, 125.78, 126.64, 128.98, 130.30, 130.51, 130.58, 131.58, 132.43, 132.49, 146.82, 149.07; exact mass, *m/z* calcd for $C_{15}H_{20}OSe$ 296.0679, found 296.0664. Anal. Calcd for $C_{15}H_{20}OSe$: C, 61.01; H, 6.83; O, 5.42. Found: C, 60.88; H, 6.77; O, 6.08.

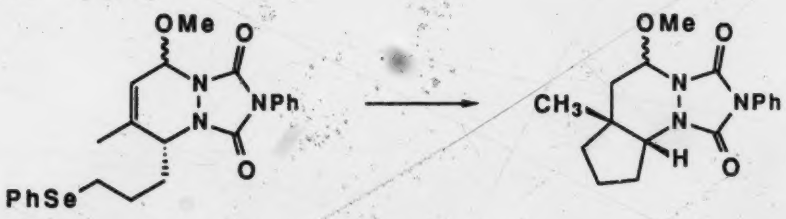
(5α,8α)- and (5α,8β)-5,8-Dihydro-5-methoxy-7-methyl-2-phenyl-8-[3-(phenylseleno)propyl]-*s*-triazolo[1,2-a]pyridazine-1,3-dione (158).



Dienes **157** (223 mg, 0.755 mmol) in ether (5 mL) were added to the triazolinedione **150** (162 mg, 0.904 mmol) in dry ether (5 mL). The color was discharged immediately. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 1:3 ethyl acetate-hexane gave **158** (246 mg, 73%) as a 1:1 mixture (^{1}H NMR, 300 MHz) of isomers that were inseparable by chromatography: FT-IR ($CHCl_3$ cast) 1785, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-2.09 (m, 3 H), 1.83 (s, 1.5 H), 1.88 (s, 1.5 H), 2.12-

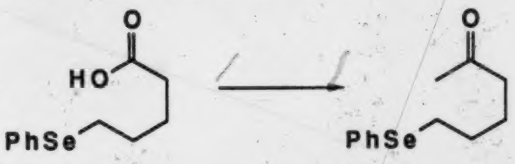
2.25 (m, 0.5 H), 2.25-2.40 (m, 0.5 H), 2.76-3.10 (m, 2 H), 3.52 (s, 1.5 H), 3.58 (s, 1.5 H), 4.47 (dd, J = 5.0, 3.0 Hz, 0.5 H), 4.54 (t, J = 4.5 Hz, 0.5 H), 5.49 (d, J = 3.0 Hz, 0.5 H), 5.51 (d, J = 4.8 Hz, 0.5 H), 5.70 (dq, J = 4.0, 1.0 Hz, 0.5 H), 5.82 (dq, J = 3.6, 0.7 Hz, 0.5 H), 7.20-7.31 (m, 3 H), 7.35-7.61 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.04, 20.32, 24.57, 24.99, 27.54, 27.64, 29.97, 31.92, 56.20, 56.91, 57.06, 58.14, 78.29, 80.00, 117.93, 118.39, 125.51, 126.89, 127.08, 128.21, 129.04, 120.10, 129.13, 130.06, 131.17, 131.41, 132.86, 132.90, 136.91, 137.78, 150.24, 150.47, 151.09, 152.15; exact mass, *m/z* calcd for $C_{23}H_{25}N_3O_3Se$ 471.1069, found 471.1064. Anal. Calcd for $C_{23}H_{25}N_3O_3Se$: C, 58.72; H, 5.36; N, 8.93; O, 10.20. Found: C, 58.91; H, 5.64; N, 8.72; O, 9.89.

(4α,5aβ,8aβ)- and (4α,5aα,8aα)-4-Methoxy-5a-methyldodecahydro-2-phenyl-2,3a,8b-triaza-*as*-indacene-1,3-dione (159).



The general procedure for radical cyclization was followed using **158** (72 mg, 0.153 mmol) in benzene (30 mL), triphenyltin hydride (50 µL, 68 mg, 0.196 mmol) in benzene (10 mL), and AIBN (4 mg, 0.024 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:3 ethyl acetate-hexane gave **159** (37.2 mg, 77%) as a 1:1 mixture (^{1}H NMR, 200 MHz) of isomers that were inseparable by chromatography: FT-IR ($CHCl_3$ cast) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 1.5 H), 1.36 (s, 1.5 H), 1.42-1.96 (m, 6 H), 2.07-2.24 (m, 1 H), 2.28-2.42 (m, 0.5 H), 2.48-2.60 (m, 0.5 H), 3.44 (s, 1.5 H), 3.48 (s, 1.5 H), 3.84 (dd, J = 6.3, 5.1 Hz, 0.5 H), 4.12 (t, J = 8.8 Hz, 0.5 H), 5.39 (dd, J = 4.7, 2.6 Hz, 0.5 H), 5.44 (dd, J = 3.4, 2.4 Hz, 0.5 H), 7.33-7.40 (m, 1 H), 7.45-7.55 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.54, 22.20, 24.92, 26.29, 28.84, 30.00, 35.03, 37.17, 37.70, 38.75, 39.32, 40.10, 57.30, 57.57, 62.55, 65.10, 81.04, 81.99, 125.44, 125.58, 128.02, 129.06, 131.41, 152.03, 152.97; exact mass, *m/z* calcd for $C_{17}H_{21}N_3O_3$ 315.1583, found 315.1584. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.70; H, 6.62; N, 13.15.

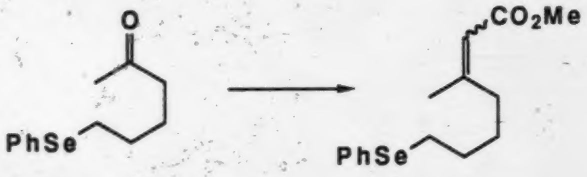
6-(Phenylseleno)-2-hexanone (161).



A general literature procedure[61] was followed. Methyllithium (1.4 M in diethyl ether, 10.0 mL, 14.0 mmol) was added over 5 min to a stirred and cooled (0°C) solution of acid **160**[55] (1.32 g, 5.13 mmol) in THF (30 mL). Stirring was continued at 0°C for 1.5 h. The reaction was quenched by addition of chlorotrimethylsilane (10.0 mL, 8.56 g, 7.88

mmol). The cooling bath was removed and after 30 min, hydrochloric acid (1 M, 30 mL) was added and stirring was continued for a further 30 min. The mixture was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 ethyl acetate-hexane gave **161** (975 mg, 74%) as a homogeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58-1.80 (m, 4 H), 2.10 (s, 3 H), 2.40 (t, J = 7.0 Hz, 2 H), 2.88 (t, J = 7.0 Hz, 2 H), 7.18-7.28 (m, 3 H), 7.42-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.68, 27.27, 29.43, 29.67, 42.81, 126.59, 128.87, 130.16, 132.34, 208.24; exact mass, *m/z* calcd for $C_{12}H_{16}OSe$ 256.0366, found 256.0365. Anal. Calcd for $C_{12}H_{16}OSe$: C, 56.47; H, 6.32; O, 6.27. Found: C, 56.44; H, 6.49; O, 6.66.

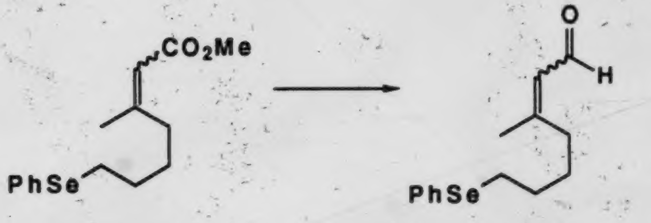
(*E*)- and (*Z*)-Methyl 3-Methyl-7-(phenylseleno)-2-heptenoate (162).



The procedure for compound **155** was followed using potassium *tert*-butoxide (600 mg, 5.347 mmol), and trimethyl phosphonoacetate (1.00 g, 5.491 mmol) in THF (20 mL). Ketone **161** (880 mg, 3.448 mmol) in THF (5 mL) was added at 0°C and the resulting mixture was stirred at room temperature for 16

h. The reaction was quenched by the addition of water (50 mL). The mixture was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with hexane gave **162** (806 mg, 75%) as a mixture (^1H NMR, 200 MHz) of isomers: FT-IR ($CHCl_3$ cast) 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.51-1.82 (m, 4 H), 1.85 (d, J = 1.4 Hz, 0.9 H), 2.08-2.18 [m, (including a doublet, J = 1.4 Hz, at 2.15),3.5 H], 2.60-2.70 (m, 0.6 H), 2.86-2.98 (m, 2 H), 3.66 (s, 0.9 H), 3.69 (s, 2.1 H), 5.62-5.68 (m, 1 H), 7.20-7.32 (m, 3 H), 7.34-7.44 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.56, 24.94, 27.26, 27.48, 27.54, 28.03, 29.47, 29.94, 32.51, 40.13, 50.67, 115.32, 115.87, 126.57, 126.70, 128.89, 128.95, 130.41, 132.45, 132.51, 159.63, 167.01; exact mass, *m/z* calcd for $C_{15}H_{20}O_2Se$ 312.0629, found 312.0632. Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.48; O, 10.28. Found: C, 57.60; H, 6.39; O, 10.14

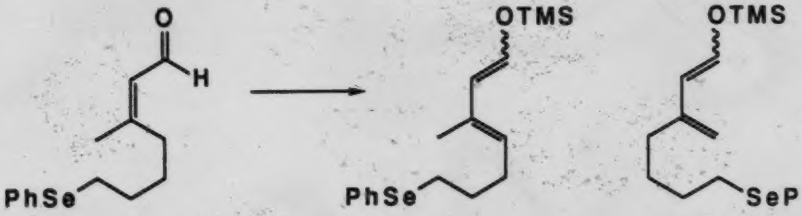
(*E*)- and (*Z*)-3-Methyl-7-(phenylseleno)-2-heptenal (163).



The procedure used for **156** was followed using esters **162** (740 mg, 2.377 mmol) and diisobutylaluminum hydride (1.0 M in dichloromethane, 5.0 mL, 5.0 mmol) in dichloromethane

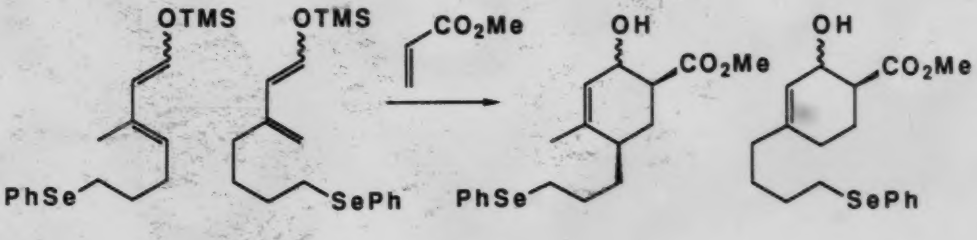
(10 mL). The crude alcohol was oxidized according to the procedure used for **156**, using DDQ (810 mg, 3.568 mmol) in dioxane (40 mL). Flash chromatography of the crude product over silica gel (3 x 15 cm) with 3:25 ethyl acetate-hexane gave **163** (359 mg, 54% from **162**) as a mixture (^{1}H NMR, 200 MHz) of isomers: FT-IR (CHCl$_3$ cast) 1671 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.62-1.83 (m, 4 H), 1.94 (d, J = 1.2 Hz, 0.8 H), 2.12 (d, J = 1.2 Hz, 2.2 H), 2.18 (t, J = 7.1 Hz, 1.5 H), 2.55 (t, J = 7.2 Hz, 0.5 H), 2.86-3.00 (m, 2 H), 5.80-5.90 (m, 1 H), 7.20 (m, 3 H), 7.42-7.53 (m, 2 H), 9.91 (d, J = 8.0 Hz, 0.3 H), 9.96 (d, 8.5 Hz, 0.7 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 17.34, 24.79, 26.96, 27.32, 27.38, 28.52, 29.46, 29.66, 31.90, 39.62, 126.79, 126.85, 127.03, 127.37, 128.47, 128.98, 130.09, 132.57, 132.65, 132.89, 190.34, 191.00; exact mass, *m/z* calcd for $C_{14}H_{18}OSe$: 282.0523, found 282.0537. Anal. Calcd for $C_{14}H_{18}OSe$: C, 59.79; H, 6.45; O, 5.69. Found: C, 59.44; H, 6.64; O, 5.82.

(1*Z*,3*E*)- and (1*E*,3*E*)-3-Methyl-7-(phenylseleno)-1-(trimethylsilyloxy)-1,3-heptadiene (164a) and (*Z*)- and (*E*)-3-[4-(Phenylseleno)butyl]-1-(trimethylsilyloxy)-1,3-butadiene (164b).



A general literature procedure was followed.[63] A solution of aldehydes **163** (800 mg, 2.840 mmol), triethylamine (0.475 mg, 3.400 mmol), chlorotrimethylsilane (0.43 ml, 3.388 mmol), and DMF (0.2 ml), in benzene (1 ml) was heated (90°C) in an oil bath for 14 h. The resulting mixture was cooled, filtered through Florisil, and the solvent was evaporated to give a mixture (^{1}H NMR, 200 MHz) of **164a** and **164b** (900 mg, 86%), which was used without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.15-0.30 (m, 9 H), 1.50-1.90 (m, [including singlets at 1.70 and 1.78], 3.8 H), 2.10-2.35 (m, 1.8 H), 2.85-3.00 (m, 2.7 H), 4.7-5.25 (m, 1.8 H), 5.70-5.80 (m, 0.5 H), 6.06-6.18 (m, 0.5 H), 6.40-6.60 (m, 0.9 H), 7.20 (m, 3 H), 7.42-7.53 (m, 2 H); exact mass, *m/z* calcd for $C_{17}H_{26}OSiSe$ 354.0918, found 354.0910.

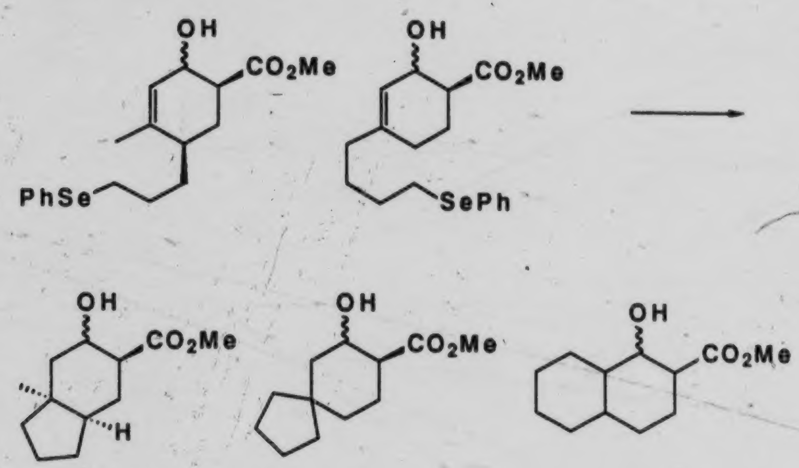
Methyl (1α,2α,5α)- and Methyl (1α,2β,5α)-2-Hydroxy-4-methyl-5-[3-(phenylseleno)propyl]-3-cyclohexene-1-carboxylate (165a) and Methyl (*cis*)- and Methyl (*trans*)-2-Hydroxy-4-[4-(phenylseleno)-butyl]-3-cyclohexene-1-carboxylate (165b).



A general literature procedure was followed.[62] A solution of methyl acrylate (250 mg, 2.904 mmol) and dienes

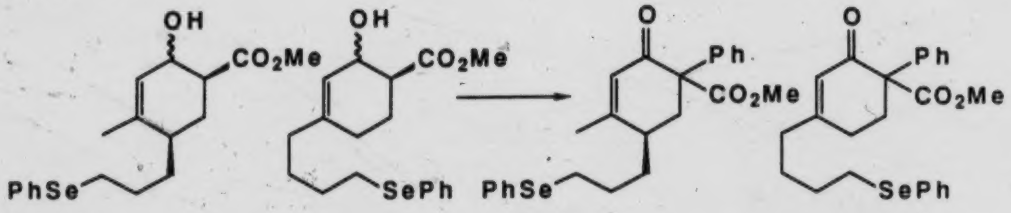
164a and **164b** (817 mg, 2.312 mmol) in dry benzene (5 ml) was sealed in a glass tube that had been flushed with argon, and was heated in an oil bath at 140°C for 15 h. After cooling, and evaporation of the solvent, the residue was dissolved in ether (10 ml) and cooled (0°C). Tetrabutylamonium fluoride (2 M in THF, 2.5 ml, 5.0 mmol) was added with stirring. After 5 min, water (5 ml) was added and the mixture was extracted with ether (2 x 5 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:3 ethyl acetate-hexane gave a mixture (^{1}H NMR, 200 MHz) of **165a** and **165b** (521 mg, 61%): FT-IR ($CHCl_3$ cast) 1735, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30-2.30 (m [including a singlet at 1.78], 10 H), 2.40-2.70 (m, 2 H), 3.00 (t, J = 6.8 Hz, 2 H), 3.81 (s, 3 H), 3.40-3.60 (m, 1 H), 5.44 (s, 0.4 H), 5.64 (d, J = 2.4 Hz, 0.4 H), 5.72 (d, J = 2.2 Hz, 0.2 H), 7.20-7.34 (m, 3 H), 7.45-7.58 (m, 2 H); exact mass, *m/z* calcd for $C_{18}H_{24}O_3Se$ 368.0890, found 369.0890.

Cyclization of 165a and 165b.



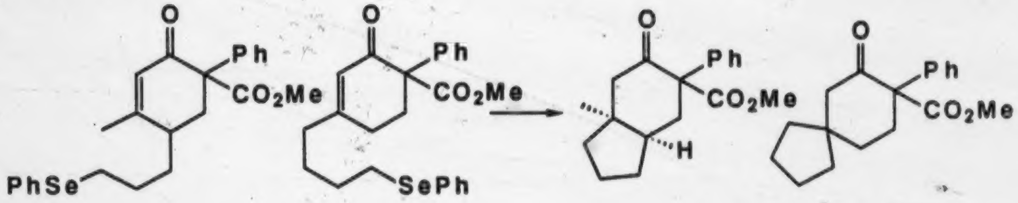
The general procedure for radical cyclization was followed using the mixture of selenides **165a** and **165b** (102 mg, 0.278 mmol) in benzene (25 mL), triphenyltin hydride (110 µL, 151 mg, 0.431 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave a complex mixture (^{1}H NMR, 400 MHz) of compounds (52 mg, 88%) of which approximately 65% was cyclized material which was determined by the integration of high field triplets corresponding to terminal methyl groups. The other products were those of simple reduction (i.e., replacement of PhSe by H in **165a** and **165b**): FT-IR (CHCl$_3$ cast) 1737, 3450 cm^{-1}; exact mass, *m/z* calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1406.

Methyl 4-Methyl-2-oxo-1-phenyl-5-[3-(phenylseleno)propyl]-3-cyclohexene-1-carboxylate (166a) and Methyl 2-Oxo-1-phenyl-4-[4-(phenylseleno)butyl]-3-cyclohexene-1-carboxylate (166b).



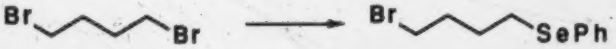
A general literature procedure was followed.[50b] A mixture of alcohols **165a** and **165b** (200 mg, 0.544 mmol) and triphenylbismuth carbonate (380 mg, 0.760 mmol) was heated in refluxing dichloromethane (4 ml) for 48 h. The resuling mixture was filtered through Celite® and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave a mixture (^{1}H NMR,200 MHz) of compounds **166a** and **166b** (150 mg, 62%): FT-IR ($CHCl_3$ cast) 1667, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45-1.66 (m, 3 H), 1.70-1.95 (m [including a singlet at 1.78], 2.5 H), 2.05-2.15 (m, 1.3 H), 2.25-2.45 (m, 0.7 H), 2.49-2.64 (m, 1.5 H), 2.74-2.95 (m, 3 H), 3.67 (s, 1 H), 3.71 (s, 2 H), 5.99 (s, 1 H), 7 12-7.35 (m, 8 H), 7.45-7.50 (m, 2 H); exact mass, *m/z* calcd for $C_{24}H_{26}O_3Se$ 442.1047, found 442.1051.

Methyl (3aα,7aα)-7a-Methyl-6-oxo-5-phenyloctahydro-1*H*-indene-5-carboxylate (167a) and Methyl 9-Oxo-8-phenylspiro[4.5]decane-8-carboxylate (167b).



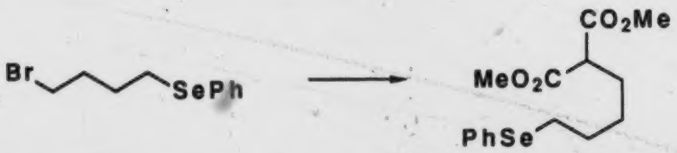
The general procedure for radical cyclization was followed using selenides **166a** and **166b** (50 mg, 0.113 mmol) in benzene (10 mL), triphenyltin hydride (55 µL, 76 mg, 0.215 mmol) in benzene (10 mL), and AIBN (6 mg, 0.036 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave a mixture (^{1}H NMR, 400 MHz) of compounds **167a** and **167b** (25 mg, 77%): FT-IR ($CHCl_3$ cast) 1715, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 0.9 H), 1.36-1.43 (m, 1.6 H), 1.45-1.54 (m, 1.7 H), 1.57-1.75 (m, 4.5 H), 1.76-2.05 (m, 1.3 H), 2.35-2.80 (m, 4 H), 3.56 (s, 1 H), 3.72 (s, 2 H), 7.20-7.41 (m, 5 H); exact mass, *m/z* calcd for $C_{18}H_{22}O_3$ 286.1568, found 286.1569.

1-Bromo-4-(phenylseleno)butane (168).



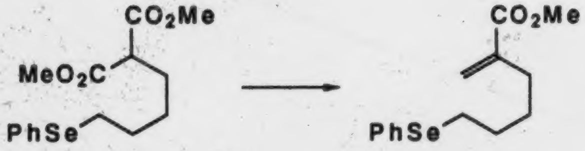
1,4-Dibromobutane (27.0 g, 125 mmol) was added to a stirred and cooled (0°C) solution of sodium phenylselenide [from diphenyl diselenide (5.80 g, 18.6 mmol) and sodium borohydride (1.50 g, 38.7 mmol) in absolute ethanol (150 mL)]. Stirring was continued at room temperature for 30 min, followed by refluxing for 1 h. The mixture was cooled and evaporated to about 10 mL. The residue was taken up in ether (200 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. Distillation of the residue afforded the excess dibromide [b.p. 65°C (3 mm Hg)] followed by **168** (5.40 g, 50%) which was an oil that slowly solidified to a wax: b.p. 112°C (0.12 mm Hg); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70-2.05 (m, 4 H), 2.90 (t, J = 6.8 Hz, 2 H), 2.39 (t, J = 6.5 Hz, 2 H), 7.20-7.30 (m, 3 H), 7.43-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.74, 28.45, 32.45, 32.91, 126.86, 129.02, 129.95, 132.64; exact mass, *m/z* calcd for $C_{10}H_{13}{}^{81}BrSe$ 292.9366, found 292.9395. Anal. Calcd for $C_{10}H_{13}BrSe$: C, 41.12; H, 4.49. Found: C, 41.49; H, 4.55.

Dimethyl 2-[4-(Phenylseleno)butyl]propanedioate (169).



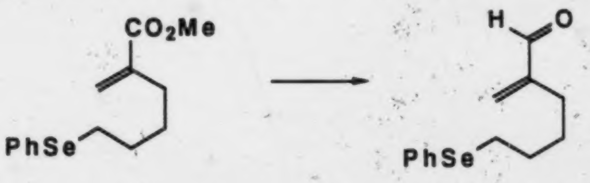
A general literature procedure[51] was followed. Bromide **168** (5.10 g, 17.46 mmol) was added to a stirred and cooled (0°C) solution of sodium dimethyl malonate [from dimethyl malonate (3.17 g, 24.00 mmol) added dropwise to sodium hydride (60% in oil, 0.80 g, 20.00 mmol) in THF (75 mL)]. The mixture was allowed to warm to room temperature, and it was then heated at reflux for 4 h. The solvent was evaporated and the residue was taken up in ether. The resultant mixture was filtered through a sintered funnel. Evaporation of the filtrate followed by flash chromatography of the residue over silica gel (5 x 15 cm) with 2:25 ethyl acetate-hexane gave **169** (4.76 g, 79%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1753, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44-1.64 (m, 2 H), 1.72-1.92 (m, 2 H), 1.92-2.10 (m, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 3.35 (t, J = 7.4 Hz, 1 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 7.23-7.37 (m, 3 H), 7.44-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.24, 27.29, 28.14, 29.56, 51.38, 52.33, 126.66, 128.90, 132.49, 169.60; exact mass, *m/z* calcd for $C_{15}H_{20}O_4Se$ 344.0534, found 344.0525. Anal. Calcd for $C_{15}H_{20}O_4Se$: C, 52.48; H, 5.87; O, 18.64. Found: C, 52.46; H, 5.84; O, 18.31.

Methyl 2-[4-(Phenylseleno)butyl]-2-propenoate (170).



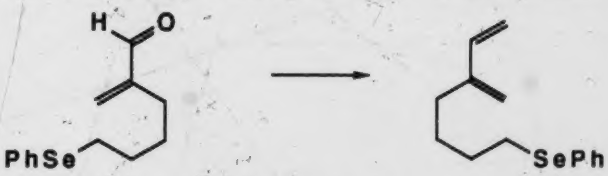
A general literature procedure[65] was followed. Potassium hydroxide (85%, 0.86 g, 13.03 mmol) in methanol (8.0 mL) was added to a stirred and cooled (0°C) solution of **169** (4.46 g, 12.99 mmol) in methanol (5 mL). The mixture was stirred at 0°C for 3.5 h. The solvent was evaporated and water (30 mL) was added. The aqueous solution was acidified using hydrochloric acid (2.0 M) and extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The resulting oil was cooled (0°C) and stirred, and diethylamine (1.00 mL, 13.66 mmol) was added dropwise over 20 min, followed by aqueous formaldehyde (37%, 1.20 mL, 15.97 mmol). Stirring was continued at room temperature for 36 h. The reaction mixture was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:20 ethyl acetate-hexane gave **170** (1.70 g, 44%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48-1.80 (m, 4 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.91 (t, J = 7.2 Hz, 2 H), 3.72 (s, 3 H), 5.50 (s, 1 H), 6.13 (s, 1 H), 7.19-7.32 (m, 3 H), 7.43-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.46, 28.36, 29.54, 31.18, 51.62, 124.70, 125.57, 128.87, 130.55, 132.43, 140.11, 167.47; exact mass, *m/z* calcd for $C_{14}H_{18}O_2Se$ 298.0472, found 298.0473. Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10; O, 10.76. Found: C, 56.68; H, 6.15; O, 10.50.

2-[4-(Phenylseleno)butyl]-2-propenal (171).



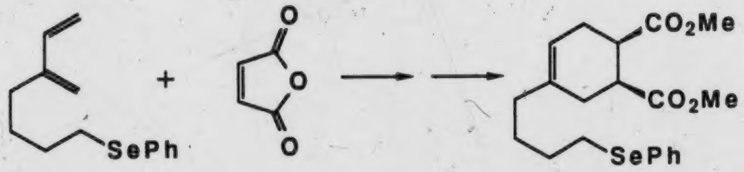
The procedure used for **156** was followed using **170** (1.36 g, 4.57 mmol) and diisobutylaluminum hydride (1.0 M in dichloromethane, 10.0 mL, 10.0 mmol) in dichloromethane (20 mL). The crude alcohol was oxidized using DDQ (1.60 g, 7.05 mmol) in dioxane (100 ml). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **171** (0.85 g, 69%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (quintet, J = 7.6 Hz, 2 H), 1.72 (quintet, J = 7.5 Hz, 2 H), 2.24 (t, J = 7.5 Hz, 2 H), 2.94 (t, J = 7.2 Hz, 2 H), 5.98 (s, 1 H), 6.23 (s, 1 H), 7.20-7.29 (m, 3 H), 7.45-7.50 (m, 2 H), 9.53 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.15, 27.43, 27.73, 29.65, 126.68, 128.96, 130.29, 132.49, 134.14, 149.76, 194.54; exact mass, *m/z* calcd for $C_{13}H_{16}OSe$ 268.0366, found 268.0364. Anal. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.04; O, 5.99. Found: C, 58.65; H, 6.13; O, 6.39.

2-[4-(Phenylseleno)butyl]-1,3-butadiene (172).



The procedure for compound **157** was followed using **171** (375 mg, 1.403 mmol), potassium *tert*-butoxide (650 mg, 5.292 mmol), and methyltriphenylphosphonium bromide (2.300 g, 6.438 mmol) in dioxane (20 mL). Flash chromatography of the crude product over silica gel (2 x 15 cm) with hexane gave **172** (356 mg, 96%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1753, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51-1.82 (m, 4 H), 2.20 (t, J = 7.2 Hz, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 4.95 (s, 1 H), 4.99 (s, 1 H), 5.04 (d, J = 10.9 Hz, 1 H), 5.20 (d, J = 17.5 Hz, 1 H), 6.35 (dd, J = 17.5, 10.9 Hz, 1 H), 7.16-7.30 (m, 3 H), 7.41-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.64, 28.11, 29.69, 30.69, 113.13, 115.73, 126.57, 128.90, 130.49, 132.40, 138.75, 145.84; exact mass, *m/z* calcd for $C_{14}H_{18}Se$ 266.0573, found 266.0571. Anal. Calcd for $C_{14}H_{18}Se$: C, 63.39; H, 6.84. Found: C, 63.37; H, 6.93.

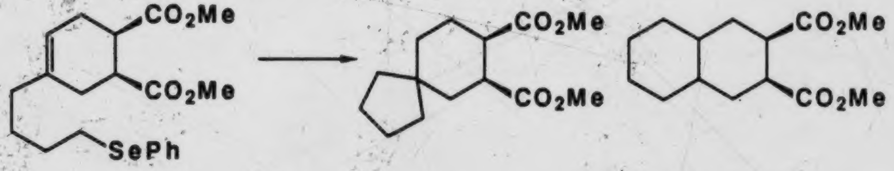
Dimethyl (*cis*)-4-[4-(Phenylseleno)butyl]-4-cyclohexene-1,2-dicarboxylate (174).



Diene **172** (207 mg, 0.780 mmol) and maleic anhydride (105 mg, 1.071 mmol) were dissolved in anhydrous benzene (5 mL) and the solution was refluxed for 6 h. Evaporation of the solvent gave the Diels-Alder adduct **173**, as an oil that hydrolysed on silica gel. A solution of the crude **173** and sulfuric acid (conc., 5 µL) in methanol (5 ml) was refluxed for 10 h. Evaporation of the solvent followed by flash chromatography of the residue over silica gel (1 x 15) with 1:9 ethyl acetate-hexane gave **174** (218 mg, 68% from diene **172**): FT-IR ($CHCl_3$ cast) 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ

1.46-1.58 (m, 2 H), 1.65 (quintet, J = 7.4 Hz, 2 H), 1.97 (t, J = 7.4 Hz, 2 H), 2.18-2.35 (m, 2 H), 2.41-2.56 (m, 2 H), 2.90 (t, J = 7.0 Hz, 2 H), 2.98 (td, J = 6.0, 3.4 Hz, 1 H), 3.02 (td, J = 6.8, 4.0 Hz, 1 H), 3.68 (s, 6 H), 5.36 (s, 1 H), 7.20-7.28 (m, 3 H), 7.44-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.74, 27.42, 27.62, 28.47, 29.51, 36.60, 39.59, 40.16, 51.74, 119.04, 126.54, 128.91, 130.53, 132.29, 135.68, 173.67, 173.69; exact mass, *m/z* calcd for $C_{20}H_{26}O_4Se$ 410.0996, found 410.0995. Anal. Calcd for $C_{20}H_{26}O_4Se$: C, 58.68; H, 6.40; O, 15.63. Found: C, 58.45; H, 6.35; O, 15.75.

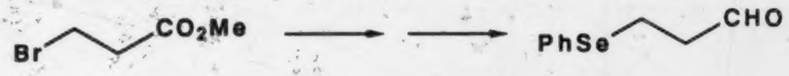
Dimethyl (*cis*)-Spiro[4.5]decane-7,8-dicarboxylate (175a) and Dimethyl (2α,3α)-Decahydronaphthalene-2,3-dicarboxylate (175b).



The general procedure for radical cyclization was followed using selenide **174** (73 mg, 0.178 mmol) in benzene (20 mL), triphenyltin hydride (75 µL, 103 mg, 0.294 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave a mixture (^1H NMR, 400 MHz) of **175a** and **175b** (47 mg, 99%) : FT-IR ($CHCl_3$ cast) 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88-1.07 (m, 1 H), 1.20-1.40 (m, 5 H), 1.57-2.00 (m, 5 H), 2.02-2.10

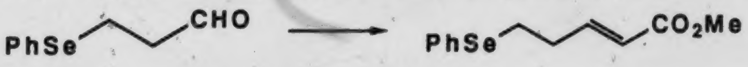
(m, 1 H), 2.48 (dt, J = 12.8, 4.0 Hz, 0.5 H), 2.63 (m, 0.5 H), 3.55 (m, 0.5 H), 3.27 (m, 0.5 H), 3.64 (s, 6 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 24.00, 24.54, 24.65, 26.24, 26.28, 31.21, 33.23, 33.29, 34.12, 35.37, 36.09, 42.12, 174.07, 174.18, 174.35, 174.65 (s and t), 38.44, 41.07, 41.50, 41.83, 42.37, 43.62, 51.53, 51.57, 51.60 (d and q); exact mass, *m/z* calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1515. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.01; H, 8.47.

3-(Phenylseleno)propanal (176).



Methyl 3-bromopropionate (2.22 g, 13.3 mmol) in absolute ethanol (5 mL) was added to a solution of sodium phenylselenide (13.4 mmol) [from diphenyl diselenide (2.0 g, 6.7 mmol) and $NaBH_4$ (0.51 g, 13.3 mmol) in absolute ethanol (50 mL)]. The mixture was stirred for 15 min and then refluxed for 2 h. The mixture was cooled, filtered, concentrated to about 10 mL, and diluted with ether (100 mL). The organic solution was washed with water (2 x 20 mL) and with brine (20 mL), dried ($MgSO_4$), and evaporated. The resulting crude methyl 3-(phenylseleno)propionate (3.018 g) was found to be about 90% pure by flash chromatography of a portion of product over silica gel (2 x 15 cm) with 2:25 ethyl acetate-hexane. The remaining crude product, (2.606 g, 11.47 mmol) in dichloromethane (25 mL), was treated with diisobutylaluminum hydride (1 M in dichloromethane, 11.0 mL, 11.0 mmol) as in the procedure used with aldehyde **154**. The reaction was quenched with water (100 mL) and the mixture was extracted with ether (3 x 150 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 2:25 ethyl acetate-hexane gave **176** (1.941 g, 86%) as a homogeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.87 (td, J = 7.0, 1.0 Hz, 2 H), 3.10 (t, J = 7.0 Hz, 2 H), 7.25-7.31 (m, 3 H), 7.46-7.54 (m, 2 H), 9.73 (d, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.90, 44.18, 127.40, 129.07, 129.20, 133.23, 200.61; exact mass, *m/z* calcd for $C_9H_{10}OSe$ 213.9897, found 213.9900. Anal. Calcd for $C_9H_{10}OSe$: C, 50.72; H, 4.73; O, 7.51. Found: C, 50.77; H, 4.73; O, 7.68.

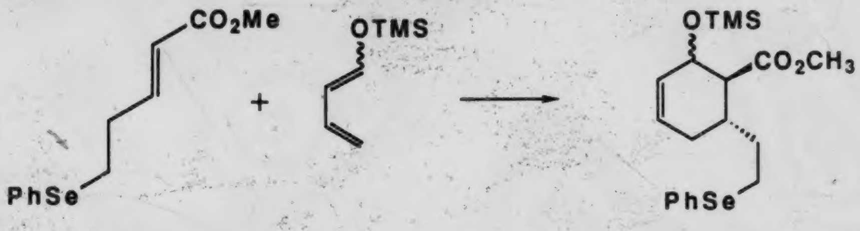
Methyl (*E*)-5-(Phenylseleno)-2-pentenoate (177).



The procedure for **155** was followed using **176** (1.22 g, 5.73 mmol), trimethyl phosphonoacetate (1.45 g, 7.96 mmol), and potassium *tert*-butoxide (0.81 g, 7.22 mmol) in dry THF (20 ml). The reaction was quenched by addition of water (20 mL), and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 1:19 ethyl acetate-hexane gave **177** (1.31 g, 85%) as a homogeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$

cast) 1723 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.59 (q, J = 7.1 Hz, 2 H), 2.99 (t, J = 7.5 Hz, 2 H), 3.74 (s, 3 H), 5.87 (dt, J = 15.5, 2.8 Hz, 1 H), 6.97 (dt, J = 15.5, 7.3 Hz, 1 H), 7.22-7.32 (m, 3 H), 7.45-7.58 (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 25.31, 32.71, 51.47, 122.10, 127.20, 129.15, 129.47, 133.16, 147.18, 166.69; exact mass, *m/z* calcd for $C_{12}H_{14}O_2Se$ 270.0159, found 270.0151. Anal. Calcd for $C_{12}H_{14}O_2Se$: C, 53.54; H, 5.24; O, 11.89. Found: C, 53.41; H, 5.24; O, 11.66.

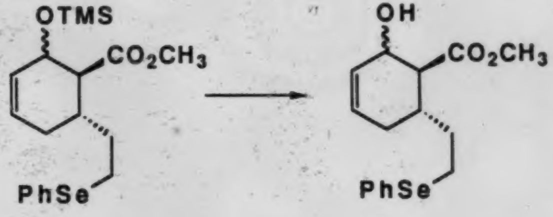
Methyl (1α,2α,6β)- and Methyl (1α,2β,6β)-6-[2-(Phenylseleno)ethyl]-2-(trimethylsilyloxy)-3-cyclohexene-1-carboxylate (179').



A solution of **177** (0.68 g, 2.53 mmol) and dienes **178**[59] (0.60 g, 2.24 mmol) in dry benzene (4 ml) was sealed in a glass tube that had been flushed with argon, and was heated in an oil bath at 180°C for 36 h. The tube was cooled and the solvent was evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with hexane (150 ml) followed by 1:30 ethyl acetate-hexane gave starting ester (241 mg) and **179'** [1.04 g, 62% (96% based on recovered **177**)] as a mixture (^{1}H NMR, 200 MHz) of isomers: FT-IR (CHCl$_3$ cast) 1735 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.00-0.20 (m, 9 H), 1.42-

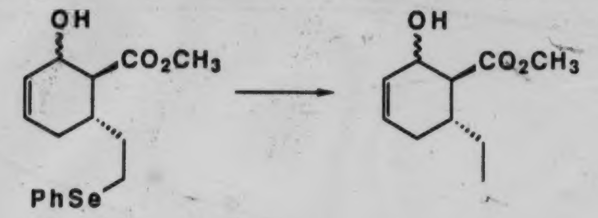
1.90 (m, 2 H), 1.95-2.50 (m, 4 H), 2.60-3.10 (m, 2 H), 3.63 (s, 1.7 H), 3.66 (s, 1.3 H), 4.41 (t, J = 3.6 Hz, 0.6 H), 4.52-4.63 (m, 0.4 H), 5.51-5.80 (m, 2 H), 7.22-7.35 (m, 3 H), 7.42-7.55 (m, 2 H); exact mass, *m/z* calcd for $C_{19}H_{28}O_3SiSe$ 312.0973, found 312.0974.

Methyl (1α,2α,6β)- and Methyl (1α,2β,6β)-2-Hydroxy-6-[2-(phenylseleno)ethyl]-3-cyclohexene-1-carboxylate (179).



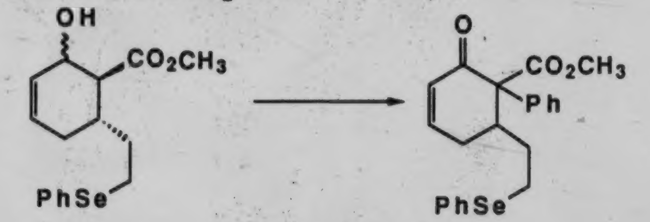
Tetrabutylammonium fluoride (1 M in THF, 0.23 ml, 0.230 mmol) was added to stirred solution of **179'** (83 mg, 0.202 mmol) in THF (1 ml). After 5 min, the solvent was evaporated and flash chromatography of the residue over silica gel (1 x 15 cm) with 1:3 ethyl acetate-hexane gave **179** (62 mg, 91%) as a mixture (^{1}H NMR, 200 MHz) of isomers: FT-IR ($CHCl_3$ cast) 1734, 3350, 3470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55-2.86 (m, 4 H), 1.95-2.35 (m, 2.7 H), 2.55 (dd, J = 9.6, 4.0 Hz, 0.3 H), 2.70-3.05 (m, 2 H), 3.63 (s, 2.1 H), 3.66 (s, 0.9 H), 4.30-4.40 (m, 0.3 H), 4.45-4.60 (m, 0.7 H), 5.60-5.85 (m, 2 H), 7.18-7.30 (m, 3 H), 7.40-7.50 (m, 2 H); exact mass, *m/z* calcd for $C_{16}H_{20}O_3Se$ 340.0578, found 340.0578.

Methyl (1α,2α,6β)- and Methyl (1α,2β,6β)-2-Hydroxy-6-ethyl-3-cyclohexene-1-carboxylate (180).



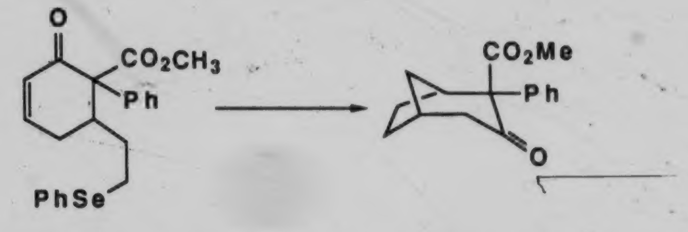
The general procedure for radical cyclization was followed using selenides **179** (50 mg, 0.147 mmol) in benzene (10 mL), triphenyltin hydride (60 µL, 82 mg, 0.235 mmol) in benzene (10 mL), and AIBN (4 mg, 0.024 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **180** (16 mg, 60%) as a mixture (^{1}H NMR, 200 MHz) of two isomers: FT-IR ($CHCl_3$ cast) 1730, 3470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) high field triplet for non-cyclized material; exact mass, *m/z* calcd for $C_{10}H_{15}O_3$ 183.1021, found 183.1017.

Methyl 2-Oxo-1-phenyl-6-[2-(phenylseleno)ethyl]-3-cyclohexene-1-carboxylate (181).



The procedure used for **166a** and **166b** was followed using alcohols **179** (200 mg, 0.589 mmol) and triphenylbismuth carbonate (400 mg, 0.800 mmol) in dichloromethane (4 ml). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **181** (100 mg, 41%) as a mixture of isomers (^{1}H NMR, 400 MHz) in a ratio of 9:1. The major isomer had: FT-IR ($CHCl_3$ cast) 1687, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.86 (m, 1 H), 2.05-2.20 (m, 1 H), 2.45-3.05 (m, 5 H), 3.72, (s, 3 H), 6.20 (d, J = 10.4 Hz, 1 H), 6.92 (m, 1 H), 6.95-7.05 (m, 2 H), 7.10-7.36 (m, 8 H); exact mass, *m/z* calcd for $C_{22}H_{22}O_3Se$ 414.0734, found 414.0765.

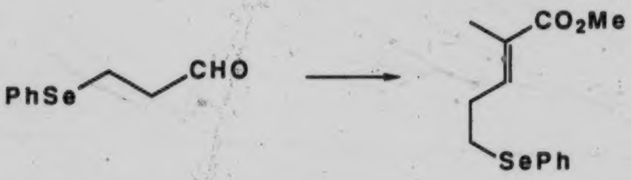
Methyl 2-Oxo-3-phenylbicyclo[3.2.1]octane-3-carboxylate (182).



The general procedure for radical cyclization was followed using selenides **181** (70 mg, 0.169 mmol) in benzene (15 mL), triphenyltin hydride (65 µL, 89 mg, 0.254 mmol) in benzene (10 mL), and AIBN (8 mg, 0.048 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave **182** (26 mg, 60%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1713, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51-1.63 (m, 2 H), 1.65-1.78 (m, 1 H), 1.83 (d, J = 12.4 Hz, 1 H), 1.91-2.00 (m, 1 H), 2.01-2.12 (m, 1 H), 2.33 (dd, J = 14.3, 2.8 Hz, 1 H), 2.39-2.45 (m, 1 H), 2.68 (ddd, J = 14.3, 3.7, 2.0 Hz, 1 H), 3.43 (m, 1 H), 3.61 (s, 3 H), 7.19-7.22 (m, 2 H), 7.25-7.30 (m, 1 H), 7.32-7.38 (m, 2 H); ^{13}C NMR

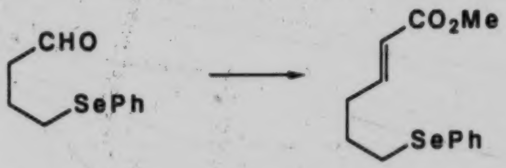
($CDCl_3$, 100.6 MHz) δ 26.61, 29.31, 34.46, 37.91, 42.85, 48.73, 52.34, 71.29, 127.44, 127.67, 128.81, 138.88 171.19, 206.66; exact mass, *m/z* calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1254.

Methyl (*E*) 2-Methyl-5-(phenylseleno)pent-2-enoate (184).



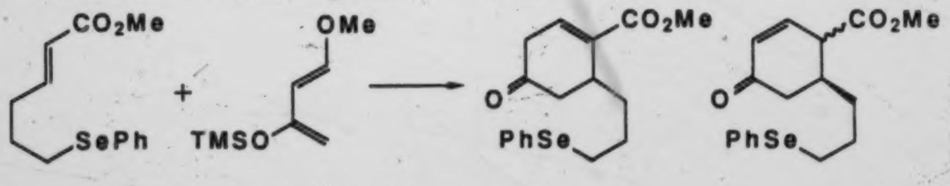
The procedure for compound **155** was followed using aldehyde **176** (500 mg, 2.346 mmol), potassium *tert*-butoxide (310 mg, 2.765 mmol), and methyl α-(dimethylphosphono)-propionate (535 mg, 2.73 mmol) in THF (8 mL). Flash chromatography of the crude product over silica gel (2 x 15 cm) with 1:20 ethyl acetate-hexane gave two separated isomers, *Z* (98 mg, 15%) and *E* (94 mg, 14%) **184**. The *Z* isomer **184** had: FT-IR ($CHCl_3$ cast) 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.79 (d, *J* = 1.5 Hz, 3 H), 2.58 (q, *J* = 7.3 Hz, 2 H), 2.98 (t, *J* = 7.4 Hz, 2 H), 3.83 (s, 3 H), 6.74 (dq, *J* = 15.3, 1.5 Hz, 1 H), 7.20-7.29 (m, 3 H), 7.46-7.55 (m, 2 H); exact mass, *m/z* calcd for $C_{13}H_{16}O_2Se$ 284.0315, found 284.0317.

Methyl (*E*)-6-(Phenylseleno)hex-2-enoate (185).



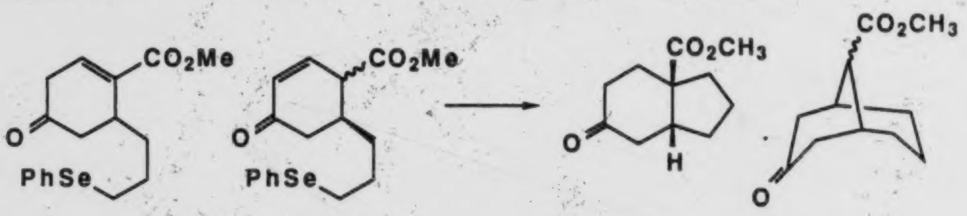
The procedure for compound **155** was followed using **154** (322 mg, 1.418 mmol), trimethyl phosphonoacetate (523 mg, 2.782 mmol), and potassium *tert*-butoxide (322 mg, 2.871 mmol) in dry THF (12 ml). The reaction was quenched by addition of water (20 mL), followed by extraction with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:24 ethyl acetate-hexane gave **185** (242 mg, 78%) as a homogeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.85 (quintet, J = 7.4 Hz, 2 H), 2.33 (q, J = 7.0 Hz, 2 H), 2.91 (t, J = 7.4 Hz, 2 H), 3.68 (s, 3 H), 5.82 (d, J = 15.5 Hz, 1 H), 6.92 (dt, J = 15.5, 7.0 Hz, 1 H), 7.20-7.29 (m, 3 H), 7.42-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.97, 28.28, 31.91, 51.33, 121.61, 126.89, 129.00, 129.79, 132.75, 147.93, 166.80; exact mass, *m/z* calcd for $C_{13}H_{16}O_2Se$ 284.0315, found 284.0324. Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.69; O, 11.30. Found: C, 55.07; H, 5.65; O, 11.24.

Methyl 4-Oxo-6-[3-(phenylseleno)propyl]-1-cyclohexene-1-carboxylate (186a) and Methyl (*cis*)- and Methyl (*trans*)-4-Oxo-6-[3-(phenylseleno)propyl]-2-cyclohexene-1-carboxylate (186b).



Ester **185** (134 mg, 0.470 mmol) and diene **183**[62] (120 mg, 0.696 mmol) were dissolved in dry benzene (3 ml). The solution was sealed in a glass tube that had been flushed with argon, and was heated in an oil bath at 180°C for 24 h. After evaporation of the solvent, the residue was dissolved in THF (6 ml) and *p*-toluenesulfonic acid (5 mg) was added. The mixture was then heated at reflux for 12 h. Water (5 ml) was added and the mixture was extracted with ether (2 x 5 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave a mixture (^1H NMR, 200 MHz) of **186a** and **186b** (98 mg, 66%) in a ratio of 3:1. The mixture had: FT-IR ($CHCl_3$ cast) 1713 cm^{-1}; exact mass, *m/z* calcd for $C_{17}H_{20}O_3Se$ 352.0578, found 352.0576. Anal. Calcd for $C_{17}H_{20}O_3Se$: C, 58.12; H, 5.74. Found: C, 57.97; H, 5.80. The major component **186a** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25-1.55 (m, 1 H), 1.45-1.85 (m, 3 H), 2.45-2.70 (m, 2 H), 2.8-2.95 (m, 2 H), 2.96 (d, J = 3.2 Hz, 1 H), 3.04 (d, J = 4.5 Hz, 1 H), 3.15-3.21 (m, 1 H), 3.78 (s, 3 H), 6.99 (dd, J = 4.7, 3.1 Hz, 1 H), 7.22-7.28 (m, 3 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.27, 27.47, 34.53, 34.88, 39.26, 43.22, 51.91, 126.82, 128.95, 132.84, 134.93, 135.52, 166.24, 207.71. One isomer of **186b** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 3.66 (s, 3 H), 6.08 (dd, J = 10.4, 2.0 Hz, 1 H), 6.78 (dd, J = 10.0, 3.0 Hz, 1 H). The other isomer of **186b** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 3.23 (s, 3 H), 6.10 (dd, J = 10.0, 2.0 Hz, 1 H), 6.94 (dd, J = 10.0, 5.0 Hz, 1 H).

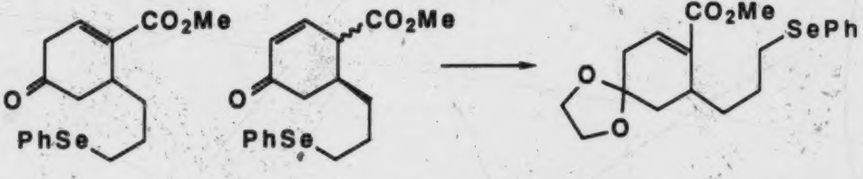
Methyl (3aα,7aα)-6-Oxooctahydro-1*H*-indene-3a-carboxylate (187a) and Methyl 3-Oxobicyclo[3.3.1]nonane-10-carboxylate (187b).



The general procedure for radical cyclization was followed using the mixture of selenides **186a** and **186b** (48 mg, 0.139 mmol) in benzene (20 mL), triphenyltin hydride (71 μL, 98 mg, 0.278 mmol) in benzene (10 mL), and AIBN (4 mg, 0.024 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave a mixture (g.c., ^{1}H NMR, 200 MHz) of two compounds (22 mg, 82%) in a ratio of 3:1. The major component **187a** had: FT-IR ($CHCl_3$ cast) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30-1.46 (m, 1 H), 1.65-1.90 (m, 4 H), 1.90-2.00 (m, 1 H), 2.09-2.17 (m, 1 H), 2.20-2.40 (m, 4 H), 2.60 (dd, J = 15.0, 6.0 Hz, 1 H), 2.69-2.77 (m, 1 H), 2.83-2.90 (m, 1 H), 3.64 (s, 3 H); exact mass, *m/z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1098. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.37; H, 8.26. Compound **187b** had: δ 0.82-0.95 (m, 1 H), 1.25-1.64 (m, 5 H), 1.80 (tt, J =

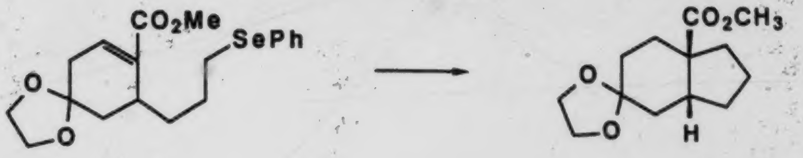
14.5, 4.1 Hz, 2 H), 2.4-2.65 (m, 3 H), 2.72-2.87 (m, 2 H), 3.78 (s, 3 H).

Methyl 4-Oxo-6-[3-(phenylseleno)propyl]-1-cyclohexene-1-carboxylate, cyclic 1,2-ethanediyl acetal (188).



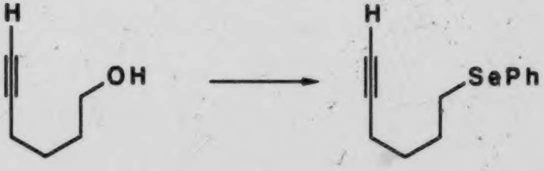
A solution of **186a** and **186b** (65 mg, 0.192 mmol), ethylene glycol (40 mg, 0.644 mmol) and *p*-toluenesulfonic acid (5 mg) in THF (10 ml) was refluxed for 12 h. Water (5 ml) was added and the mixture was extracted with ether (2 x 5 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **188** (55 mg, 73%) as a homogeneous (^1H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.80 (m, 6 H), 2.30-2.50 (m, 2 H), 2.68-2.96 (m, 4 H), 3.63 (s, 3 H), 3.90-4.00 (m, 4 H), 6.75 (dd J = 4.5, 3.0 Hz, 1 H), 7.22-7.28 (m, 3 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.76, 33.19, 34.43, 34.85, 34.85, 36.21, 51.53, 64.20, 64.59, 107.44, 126.62, 128.95, 130.59, 132.44, 135.90, 167.44; exact mass, *m/z* calcd for $C_{19}H_{24}O_4Se$ 396.0840, found 396.0863.

Methyl (3aα,7aα)-6-)-Oxooctahydro-1*H*-indene-3a-carboxylate, cyclic 1,2-ethanediyl acetal (189).



The general procedure for radical cyclization was followed using selenide **188** (33 mg, 0.083 mmol) in benzene (10 mL), triphenyltin hydride (30 μL, 41 mg, 0.117 mmol) in benzene (10 mL), and AIBN (3 mg, 0.018 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **189** (19 mg, 95%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.80 (m, 10 H), 1.90-2.09 (m, 2 H), 2.58-2.63 (m, 1 H), 3.67 (s, 3 H), 3.90-4.00 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.68, 24.98, 28.12, 29.47, 31.33, 34.19, 34.84, 41.24, 51.84, 63.88, 64.28, 108.69, 177.92; exact mass, *m/z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1098.

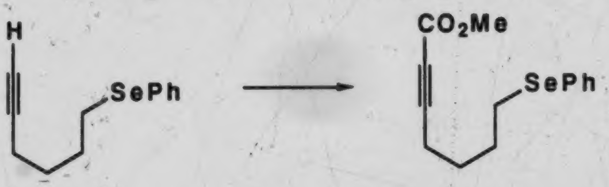
1-Phenylseleno-5-hexyne (191).



The procedure used for compound **143** was followed using 5-hexyn-1-ol (**190**) (505 mg, 5.154 mmol), phenylselenocyanate, (1.20 g, 6.62 mmol), tributylphosphine (1.45 mL, 1.18 g, 6.22

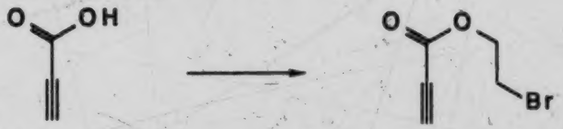
mmol) in THF (15 mL). Flash chromatography of the crude product over silica gel (3 x 15 cm) with hexane gave **191** (647 mg, 54%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 2120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65-1.95 (m, 4 H), 1.97 (t, J = 2.7 Hz, 1 H), 2.15 (td, J = 6.9, 2.7 Hz, 2 H), 2.97 (t, J = 7.3 Hz, 2 H), 7.20-7.35 (m, 3 H), 7.47-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.91, 27.25, 28.30, 29.09, 68.64, 83.98, 126.77, 129.03, 130.35, 132.60; exact mass, *m/z* calcd for $C_{12}H_{14}Se$ 238.0260, found 238.0262. Anal. Calcd for $C_{12}H_{14}Se$: C, 60.76; H, 5.95. Found: C, 60.82; H, 6.04.

Methyl 7-(Phenylseleno)-2-heptynoate (192).



n-Butyllithium (1.4 M in hexanes, 0.5 mL, 0.700 mmol) was added dropwise to a stirred and cooled (-30°C) solution of **191** (166 mg, 0.700 mmol) in THF (1 mL). After 5 min, carbon dioxide gas was bubbled through the reaction mixture for 10 min, and then the cold bath was removed and addition of carbon dioxide was continued for another 10 min. The resulting mixture was then added to ether (5 mL), acidified with hydrochloric acid (1 M, 5 mL), and the aqueous phase was extracted with ether (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was then treated with diazomethane (*ca*. 0.3 M in ether, 5 mL, 1.5 mmol). Evaporation of the resulting mixture, followed by flash chromatography of the residue over silica gel (1 x 15 cm) with 1:12 ethyl actate-hexane gave **192** (175 mg, 85%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1719, 2235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63-1.93 (m, 4 H), 2.35 (t, J = 6.7 Hz, 2 H), 2.95 (t, J = 6.9 Hz, 2 H), 3.77 (s, 3 H), 7.20-7.35 (m, 3 H), 7.47-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.17, 27.06, 27.40, 29.07, 52.54, 73.24, 89.01, 116.64, 126.89, 129.06, 130.07, 132.73, 154.12; exact mass, *m/z* calcd for $C_{14}H_{16}O_2Se$ 296.0316, found 296.0316.

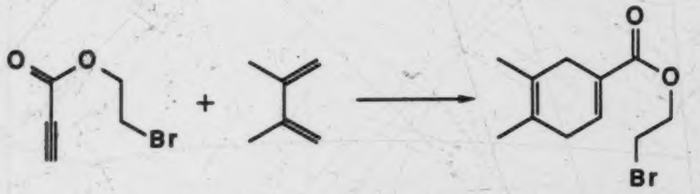
2-Bromoethyl propiolate (193).



A general literature procedure was followed.[85] *N,N*-Dicyclohexylcarbodiimide (11.78 g, 57.10 mmol) and DMAP (150 mg) were added to a stirred and cooled (0°C) solution of propiolic acid (2.00 g, 28.55 mmol) and 2-bromoethanol (3.62 g, 29.00 mmol). The mixture was allowed to warm to room temperature, and stirring was continued for 15 h. The resulting mixture was filtered and the precipitate was washed with ether (100 ml). The filtrate was washed with hydrochloric acid (2 M, 50 ml), saturated aqueous sodium bicarbonate (50 ml), brine (50 ml), and dried ($MgSO_4$). Evaporation of the solvent and distillation [90°C (0.6 mm

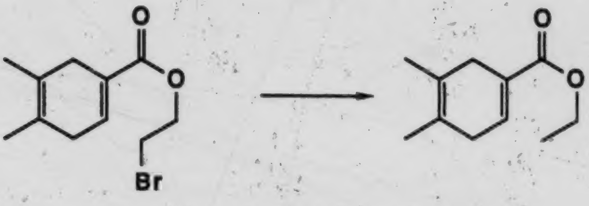
Hg)] of the residue, followed by flash chromatography of the distillate over silica gel (4 x 15 cm) with 1:19 ethyl acetate-hexane gave **193** (3.00 g, 59%) as a homogeneous (^{1}H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1720, 2120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.07 (s, 1 H), 3.56 (td, J = 5.8, 2.4 Hz, 2 H), 4.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.52, 65.10, 73.94, 75.84, 151.90; exact mass, *m/z* calcd for $C_5H_5O_2{}^{81}Br$ 268.0366, found 268.0364.

2-Bromoethyl 4,5-Dimethyl-1,4-cycloxhexadiene-1-carboxylate (194).



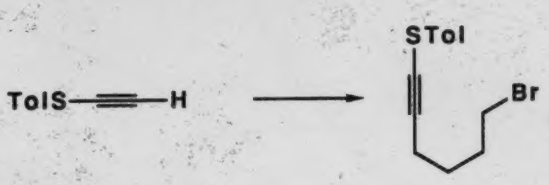
Propiolate **193** (195 mg, 1.102 mmol) and 2,3-dimethyl-1,4-butadiene (110 mg, 1.322 mmol) were dissolved in dry benzene (3 mL). The solution was sealed in a glass tube that had been flushed with argon, and was heated in an oil bath at 140°C for 20 h. The mixture was cooled and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:19 ethyl acetate-hexane gave **194** (222 mg, 78%) as a homogeneous (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67 (s, 3 H), 1.70 (s, 3 H), 2.32 (s, 1 H), 3.84 (s, 3 H), 3.57 (t, J = 6.0 Hz, 2 H), 4.47 (t, J = 6.0 Hz, 2 H), 6.90-7.06 (m, 1 H); exact mass, *m/z* calcd for $C_{11}H_{15}{}^{81}BrO_2$ 260.0235, found 260.0227.

Ethyl 4,5-Dimethyl-1,4-cycloxhexadiene-1-carboxylate (195).



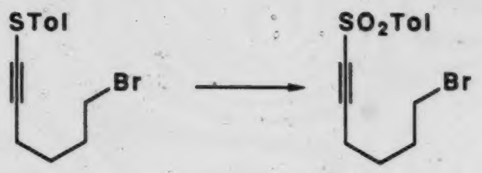
The general procedure for radical cyclization was followed using bromide **194** (113 mg, 0.436 mmol) in benzene (30 mL), triphenyltin hydride (220 µL, 302 mg, 0.861 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). The residue was taken up in ether (ca 20 mL) and stirred with an aqueous solution (10 mL) containing an excess of potassium fluoride. The precipitated tributyltin fluoride was removed by filtration, and the ether layer was separated, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:19 ethyl acetate-hexane gave **195** (68 mg, 87%) as a homogeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, J = 6.9 Hz, 3 H), 1.66 (s, 3 H), 1.69 (s, 3 H), 2.32 (s, 1 H), 3.22 (s, 3 H), 4.21 (q, J = 6.9 Hz, 2 H), 6.90-7.00 (1 H); exact mass, *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1145.

6-Bromo-1-[(4-methylphenyl)thio]-1-hexyne (196).



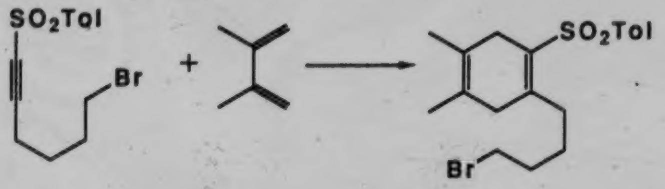
n-Butyllithium (1.6 M in hexanes, 3.7 mL, 5.92 mmol) was added over 5 min to a stirred solution of *p*-toluenethioacetylene[67] (850 mg, 5.73 mmol) in dry THF (15 mL). After 10 min, the resulting solution was added over 5 min to a stirred solution of 1,4-dibromobutane (3.70 g, 17.14 mmol) in dry THF (10 mL). The mixture was heated at 50°C for 3 h, during which time a precipitate of lithium bromide formed. Evaporation of the solvent followed by flash chromatography of the residue over silica gel (4 x 15 cm) with 1:99 ethyl acetate-hexane gave **196** (513 mg, 32%) as a homogeneous (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.76 (quintet, J = 7.1 Hz, 2 H), 2.00 (quintet, J = 7.0 Hz, 2 H), 2.32 (s, 3 H), 2.49 (t, J = 7.0 Hz, 2 H), 3.44 (t, J = 6.5 Hz, 2 H), 3.44 (t, J = 6.5 Hz, 2 H), 7.13 (d, J = 7.9 Hz, 2 H), 7.20 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.45, 20.90, 27.03, 31.65, 33.02, 66.30, 97.95, 126.23, 129.66, 129.86, 136.21; exact mass, *m/z* calcd for $C_{13}H_{15}{}^{81}BrS$ 284.0058, found 284.0048. Anal. Calcd for $C_{13}H_{15}BrS$: C, 55.13; H, 5.34; S, 11.32. Found: C, 55.15; H, 5.51; S, 11.32.

6-Bromo-1-[4-(methylphenyl)sulfonyl]-1-hexyne (197).



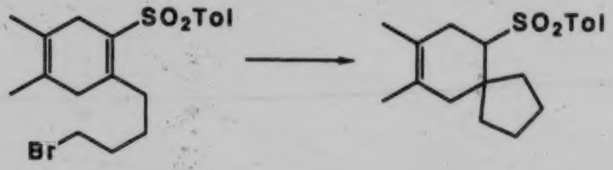
A general literature procedure[68] was followed. *m*-Chloroperbenzoic acid (85%, 615 mg, 3.029 mmol) was added to a stirred and cooled (0°C) solution of **196** (405 mg, 1.430 mmol) in chloroform (4 mL). The mixture was allowed to warm to room temperature, stirred for 16 h, taken up in ether (10 mL) and washed with saturated aqueous sodium bisulfite (2 x 5 mL), saturated aqueous sodium bicarbonate (5 mL), water (5 mL), and brine (5 mL). The organic solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 2:5 ethyl acetate-hexane gave **197** (415 mg, 92%) as a homgeneous (^1H NMR, 200 MHz) oil: FT-IR ($CHCl_3$ cast) 2200 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.65-1.76 (m, 2 H), 1.86-1.94 (m, 2 H), 2.41 (t, J = 6.8 Hz, 2 H), 2.46 (s, 3 H), 3.47 (t, J = 6.8 Hz, 2 H),7.37 (d, J = 8.0 Hz, 2 H), 7.87 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.12, 21.65, 25.40, 31.30, 32.36, 78.97, 95.68, 127.24, 129.69, 138.95, 145.20; exact mass, *m/z* calcd for $C_{13}H_{15}{}^{81}BrO_2S$ 315.9946, found 315.9939. Anal. Calcd for $C_{13}H_{15}BrO_2S$: C, 49.53; H, 4.80; O, 10.15; S, 10.17. Found: C, 49.80; H, 4.87; O, 9.99; S, 10.35.

2-(4-Bromobutyl)-4,5-dimethyl-1-[4-(methylphenyl)sulfonyl]cyclohexa-1,4-diene (198).



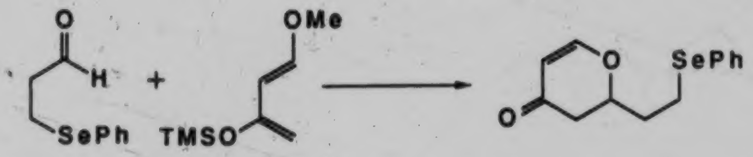
Sulfone **197** (178 mg, 0.565 mmol) and 2,3-dimethyl-1,4-butadiene (60 mg, 0.730 mmol) were dissolved in dry benzene (3 mL). The solution was sealed in a glass tube that had been flushed with argon, and was heated in an oil bath at 140°C for 20 h. The mixture was cooled and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:9 ethyl acetate-hexane gave **198** (187 mg, 83%) as a homogeneous (^{1}H NMR, 200 MHz) oil. Crystallization from dichloromethane-hexane gave a homogeneous (^{1}H NMR, 200 MHz) white solid: mp 98-102°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54-1.72 (m, 2 H), 1.64 (broad s, 6 H), 1.92 (quintet, J = 7.1 Hz, 2 H), 2.46 (s, 3 H), 2.66 (t, J = 8.0 Hz, 2 H), 2.82 (t, J = 7.0 Hz, 2 H), 2.94 (t, J = 7.5 Hz, 2 H), 3.42 (t, J = 6.6 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.50, 17.84, 21.52, 27.08, 32.14, 32.54, 33.49, 34.16, 40.13, 121.33, 122.51, 127.09, 129.64, 131.56, 138.68, 143.85, 147.93; exact mass, *m/z* calcd for $C_{19}H_{25}{}^{81}BrO_2S$ 398.0735, found 398.0738. Anal. Calcd for $C_{19}H_{25}BrO_2S$: C, 57.43; H, 6.34; Br, 20.11; S, 8.07. Found: C, 57.39; H, 6.02; Br, 20.23; S, 8.09.

8,9-Dimethyl-6-[(4-methylphenyl)sulfonyl]-spiro[4.5]dec-8-ene (199).



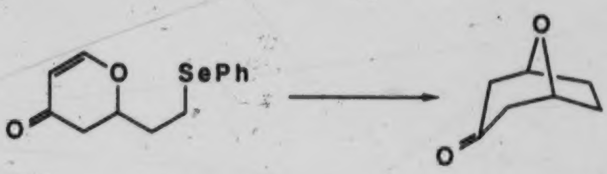
The general procedure for radical cyclization was followed using **198** (103 mg, 0.259 mmol) in benzene (20 mL), triphenyltin hydride (100 µL, 137 mg, 0.390 mmol) in benzene (10 mL), and AIBN (6 mg, 0.036 mmol) in benzene (10 mL). The reaction was worked up according to the procedure used for compound **195**. Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave **199** (50 mg, 61 %): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 3 H), 1.51 (s, 3 H), 1.60-1.86 (m, 8 H), 1.98-2.06 (m, 2 H), 2.12 (d, J = 10.0 Hz, 1 H), 2.36 (d, J = 10.0 Hz, 1 H), 2.43 (s, 3 H), 3.14 (t, J = 5.7 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.42, 18.91, 21.51, 23.30, 24.44, 32.05, 35.24, 38.98, 42.63, 44.75, 69.19, 121.26, 125.48, 128.45, 129.34, 137.76, 143.96; exact mass, *m/z* calcd for $C_{19}H_{26}O_2S$ 318.1653, found 318.1643. Anal. Calcd for $C_{19}H_{26}O_2S$: C,71.66; H, 8.23; S, 10.07. Found: C, 71.69; H, 8.11; S, 10.05.

2-[2-(Phenylseleno)ethyl]-2,3-dihydropyran-4-one (200).



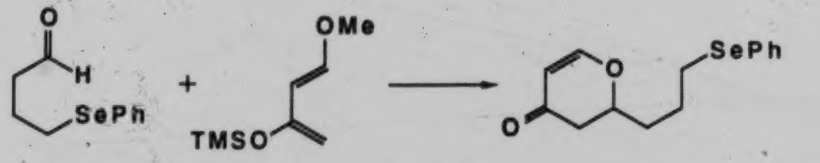
A general literature procedure[69] was followed. Boron trifluoride etherate (93 µL, 0.746 mmol) was added to a stirred and cooled (-78°C) solution of aldehyde **176** (159 mg, 0.746 mmol) and diene **183** (160 mg, 0.928 mmol) in dry dichloromethane (10 mL). After 2 h at -78°C, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (5 mL), and the mixture was extracted with ether (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Trifluoroacetic acid (1% w/v in CCl_4, 10 mL) was added to the residue. After 5 min, ether (10 mL) was added and the organic solution was washed with aqueous sodium bicarbonate (5% w/w, 5.0 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave **200** (120 mg, 57%; 72% based on conversion) as a homogeneous (^{1}H NMR, 200 MHz) oil, along with starting aldehyde **176** (34 mg). Compound **200** had: FT-IR ($CHCl_3$ cast) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85-2.06 (m, 1 H), 2.14-2.32 (m, 1 H), 2.38 (ddd, J = 16.8, 4.5, 1.1 Hz, 1 H), 2.54 (dd, J = 16.8, 12.2 Hz, 1 H), 2.91-3.16 (m, 2 H), 4.57 (octet, J = 4.1 Hz, 1 H), 5.40 (dd, J = 6.0, 1.1 Hz, 1 H), 7.20-7.36 (m, 3 H), 7.32 (d, J = 6.0 Hz, 1 H), 7.45-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.47, 34.65, 41.53, 78.41, 107.16, 127.20, 129.16, 129.32, 132.67, 162.79, 191.93; exact mass, *m/z* calcd for $C_{13}H_{14}O_2Se$ 282.1067, found 282.1030. Anal. Calcd for $C_{13}H_{14}O_2Se$: C, 55.52; H, 5.02; O, 11.38. Found: C, 55.59; H, 4.98; O, 11.62.

8-Oxabicyclo[3.2.1]octan-3-one (201).[71]



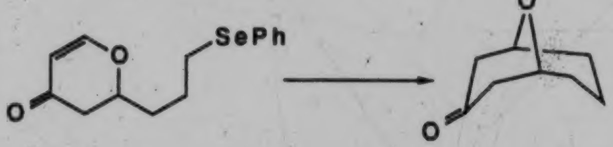
The general procedure for radical cyclization was followed using **200** (50 mg, 0.178 mmol) in benzene (20 mL), triphenyltin hydride (90 μL, 124 mg, 0.352 mmol) in benzene (10 mL), and AIBN (5 mg, 0.03 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **201** (20 mg, 89%) as a homogeneous (^1H NMR) oil: FT-IR ($CHCl_3$ cast) 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.73-1.84 (m, 2 H), 2.05-2.14 (m, 2 H), 2.3 (d, J = 16 Hz, 2 H), 2.61 (dd, J = 16.0, 5.5 Hz, 2 H), 4.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.46, 49.67, 74.79, 207.54; exact mass, *m/z* calcd for $C_7H_{10}O_2$ 126.0680, found 126.0684. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99;. Found: C, 65.86; H, 8.15.

2-[3-(Phenylseleno)propyl]-2,3-dihydropyran-4-one (202).



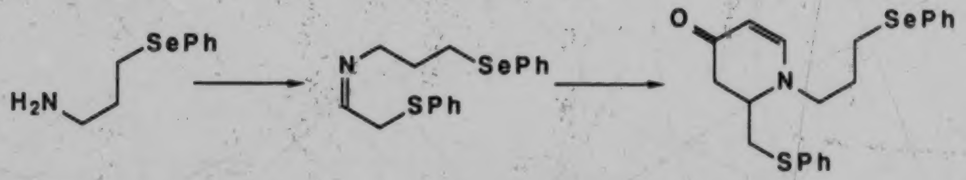
The procedure for compound **200** was followed, using aldehyde **154** (26 mg, 0.114 mmol), diene **183** (45 mg, 0.261 mmol) and boron trifluoride etherate (14 µL, 0.113 mmol) in dry dichloromethane (1.0 mL) at -78°C. Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave **202** (28 mg, 83%): FT-IR ($CHCl_3$ cast) 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70-2.05 (m, 4 H), 2.38 (ddd, J = 16.5, 4.8, 1.0 Hz, 1 H), 2.59 (dd, J = 16.5, 12.8 Hz, 1 H), 2.86 (t, J = 7.0 Hz, 2 H), 4.31-4.58 (m, 1 H), 5.40 (dd, J = 6.0, 1.0 Hz, 1 H), 7.22-7.33 (m, 3 H), 7.33 (d, J = 6.0 Hz, 1 H), 7.45-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.33, 27.27, 34.17, 41.74, 78.85, 106.98, 126.97, 129.05, 129.79, 132.76, 163.00, 192.27; exact mass, *m/z* calcd for $C_{14}H_{16}O_2Se$ 296.0323, found 296.0322. Anal. Calcd for $C_{14}H_{16}O_2Se$: C, 56.96; H, 5.46; O, 10.84. Found: C, 56.93; H, 5.36; O, 10.97.

9-Oxabicyclo[3.3.1]nonan-3-one (203).



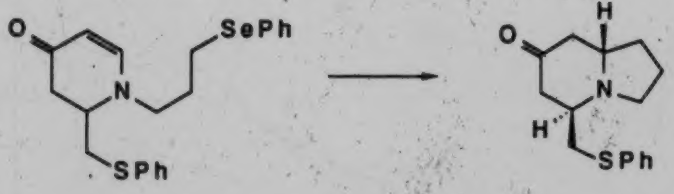
The general procedure for radical cyclization was followed using **202** (53.7 mg, 0.182 mmol) in benzene (20 mL), triphenyltin hydride (95 μL, 131 mg, 0.373 mmol) in benzene (10 mL), and AIBN (5 mg, 0.03 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave **203** (25.5 mg, 99%) as a homogeneous (^{1}H NMR, 200 MHz) white solid: mp 76-80°C; FT-IR ($CHCl_3$ cast) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.55-1.62 (m, 4 H), 1.93-2.04 (m, 2 H), 2.36 (d, J = 16.0 Hz, 2 H), 2.78 (dd, J = 16.0, 7.3 Hz, 2 H), 4.47 (dd, J = 7.3, 4.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.17, 30.50, 46.03, 69.61, 208.59; exact mass, *m/z* calcd for $C_8H_{12}O_2$ 140.0837, found 140.0836. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.06; H, 8.67.

1-[3-(Phenylseleno)propyl]-2-[(phenylthio)methyl]-2,3-dihydropyridin-4-one (206).



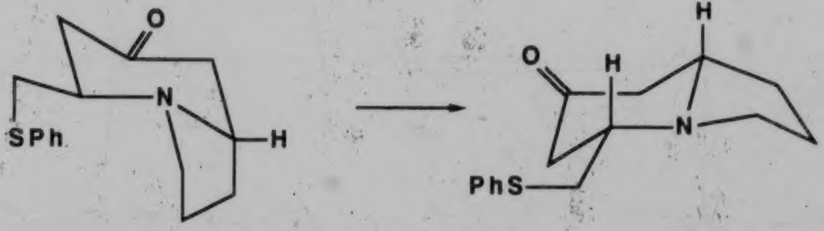
A mixture of amine **204**[40a] (300 mg, 1.401 mmol), (phenylsulphonyl)acetaldehyde[74] (215 mg, 1.417 mmol), and $MgSO_4$ (*ca* 100 mg) in THF (4 mL) was stirred at room temperature for 1 h. The resulting mixture was filtered giving a solution of the corresponding imine **205** in THF. This solution was used without purification. At this point a general literature procedure was followed.[70] A solution of diene **183** (730 mg, 4.236 mmol) and anhydrous zinc chloride (195 mg, 1.436 mmol) in THF (10 mL) was added to the above imine. After the mixture had been stirred for 48 h, the reaction was quenched by addition of water (20 mL) and the resulting mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 3:1 ethyl acetate-hexane gave **206** (230 mg, 43% from amine **204**) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1583, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75-1.86 (m, 2 H), 2.57-2.69 (m, 2 H), 2.75-2.89 (m, 2 H), 3.05 (dd, J = 13.5, 8.0 Hz, 1 H), 3.18-3.37 (m, 3 H), 3.43-3.50 (m, 1 H), 4.91 (dd, J = 7.5, 0.4 Hz, 1 H), 6.82 (dd, J = 7.5, 1.0 Hz, 1 H), 7.20-7.36 (m, 8 H), 7.40-7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.92, 29.34, 32.54, 38.58, 53.43, 55.23, 97.50, 126.64, 127.11, 128.87, 128.99, 129.63, 132.74, 134.59, 151.77, 189.31; exact mass, m/z calcd for $C_{21}H_{23}NOSSe$ 417.0665, found 417.0659.

(*cis*)-5-[(Phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone (207a).



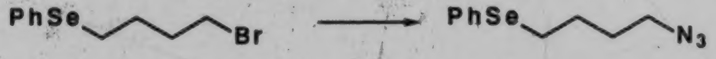
The general procedure for radical cyclization was followed using selenide **206** (90 mg, 0.234 mmol) in benzene (20 mL), triphenyltin hydride (90 µL, 124 mg, 0.352 mmol) in benzene (10 mL), and AIBN (8 mg, 0.048 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 3:1 ethyl acetate-hexane gave **207a** (45 mg, 74%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.60 (m, 1 H), 1.84-2.03 (m, 2 H), 2.05-2.16 (m, 1 H), 2.29 (dd, J = 14.0, 11.0 Hz, 1 H), 2.39 (ddd, J = 14.0, 3.6, 1.1 Hz, 1 H), 2.59 (ddd, J = 14.5, 4.4, 1.1 Hz, 1 H), 2.69-2.81 (m, 2 H), 2.85-2.92 (m, 1 H), 2.96-3.04 (m, 1 H), 3.25 (dd, J = 13.0, 4.5 Hz, 1 H), 3.26-3.34 (m, 1 H), 3.51 (sextet, J = 4.6 Hz, 1 H), 7.20-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.47, 31.70, 34.79, 41.19, 42.60, 45.65, 49.35, 55.80, 56.49, 126.16, 128.88, 129.38, 209.33; exact mass, *m/z* calcd for $C_8H_{12}NO$ (M - $CH_2SC_6H_5$) 138.0920, found 138.0920. Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.92; H, 7.33; N, 5.36; S, 12.27. Found: C, 68.42; H, 7.39; N, 5.43; S, 12.34.

(*trans*)-5-[(Phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone (207b).



After a week at room temperature, compound **207a** had partially isomerized, the ratio **207a**:**207b** being 3:2 (^{1}H NMR, 400 MHz). The isomers were separated by flash chromatography over silica gel with 2:1 ethyl acetate-hexane. Compound **207b** had: FT-IR (CHCl$_3$ cast) 1721, 2793 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.50-1.63 (m, 1 H), 1.75-2.05 (m, 3 H), 2.15-2.22 (m, 1 H), 2.29-2.40 (m, 2 H), 2.47-2.71 (m, 4 H), 3.13 (ABq, J = 12.9, 6.8 Hz, 1 H), 3.19 (ABq, J = 12.9, 3.2 Hz, 1 H), 3.36 (td, J = 8.8, 2.3 Hz, 1 H), 7.16-7.45 (m, 5 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 21.46, 30.67, 39.03, 45.17, 46.94, 50.38, 60.12, 63.63, 126.21, 128.99, 129.40, 136.40, 208.58.

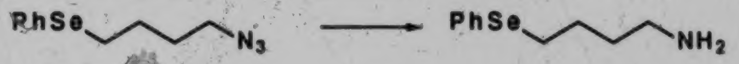
4-Azido-1-(phenylseleno)butane (208).



A solution containing bromide **168** (2.60 g, 8.90 mmol) and sodium azide (1.20 g, 1.85 mmol) in dry DMF (50 mL), was stirred at room temperature for 2 h. The mixture was diluted with ether (200 mL) and the organic phase was washed sequentially with water (2 x 100 mL), hydrochloric acid (1 M, 2 x 100 mL), water (100 mL), and brine (100 mL). The ether layer was dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 1:19 ethyl acetate-hexane gave **208** (2.15 g, 95%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR (CHCl$_3$ cast) 2096 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.60-1.80 (m, 4 H), 2.89 (t, J = 7.0 Hz, 2 H), 3.22 (t, J = 6.7 Hz, 2 H), 7.20-7.26 (m, 3 H), 7.45-7.51

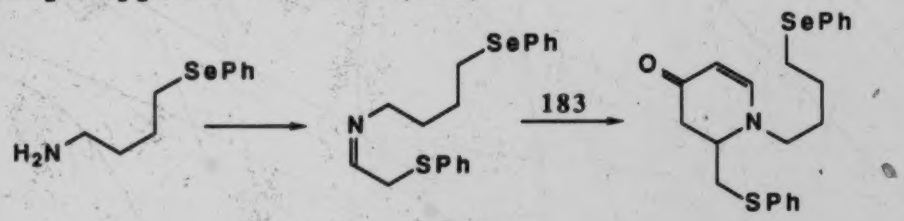
(m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.01, 27.09, 28.68, 50.68, 126.72, 128.90, 129.95, 132.51; exact mass, *m/z* calcd for $C_{10}H_{13}N_3Se$ 255.0274, found 255.0272. Anal. Calcd for $C_{10}H_{13}N_3Se$: C, 47.25; H, 5.16; N, 16.53. Found: C, 47.02; H, 5.14; N, 17.19.

4-(Phenylseleno)butylamine (209).[40a]



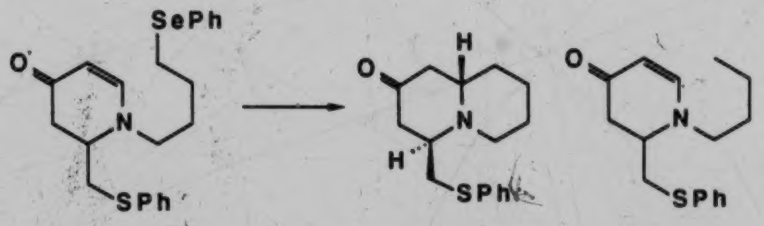
A solution of azide **208** (2.10 g, 8.26 mmol) in ether (5 mL) was added dropwise to a stirred and cooled (0°C) suspension of lithium aluminum hydride (630 mg, 16.60 mmol) in ether (15 mL). The resulting mixture was allowed to warm to room temperature over a period of 1 h. The reaction was quenched by sequential additon of water (0.65 mL), aqueous sodium hydroxide (15%, 0.65 mL), and water (2 mL). The resulting mixture was filtered, and the solvent was evaporated. The crude product was purified by distillation to give **209** as a homogeneous (^1H NMR, 400 MHz) oil (1.32 g, 70%) that solidified upon exposure to air: bp 70°C (0.1 mm Hg); FT-IR ($CHCl_3$ cast) 2750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 2 H), 1.50-1.58 (m, 2 H), 1.69-1.77 (m, 2 H), 2.68 (t, J = 6.9 Hz, 2 H), 2.91 (t, J = 7.2 Hz, 2 H), 7.20-7.26 (m, 3 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.42, 27.60, 33.82, 41.58, 126.58, 128.88, 130.37, 132.38; exact mass, *m/z* calcd for $C_{10}H_{15}NSe$ 229.0370, found 229.0368.

1-[4-(Phenylseleno)butyl]-2-[(phenylthio)methyl]-2,3-dihydropyridin-4-one (210).



The procedure for compound **205** was followed using amine **209** (200 mg, 0.876 mmol) and (phenylthio)acetaldehyde (135 mg, 0.886 mmol) in THF (2 mL). A solution of diene **183** (450 mg, 2.612 mmol) and zinc chloride (120 mg, 0.880 mmol) in THF (7 mL) was added to the resulting solution of imine **209'** in THF. After being stirred for 48 h, the reaction was quenched by addition of water (10 mL), and the resulting mixture extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 4:1 ethyl acetate-hexane gave **210** (80 mg, 21% from amine **209**) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1582, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58-1.70 (m, 4 H), 2.54-2.67 (m, 2 H), 2.79-2.89 (m, 2 H), 3.02-3.15 (m, 2 H), 3.20-3.28 (m, 2 H), 3.43-3.50 (m, 1 H), 4.90 (d, J = 7.2, 1 H), 6.80 (dd, J = 7.2, 1.0 Hz, 1 H), 7.20-7.37 (m, 8 H), 7.43-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.77, 27.02, 29.45, 32.89, 38.89, 54.02, 55.39, 97.63, 126.81, 127.10, 129.08, 129.13, 129.54, 129.87, 132.83, 134.90, 151.54, 189.40; exact mass, *m/z* calcd for $C_{22}H_{25}NOSSe$ 431.0823, found 431.0819.

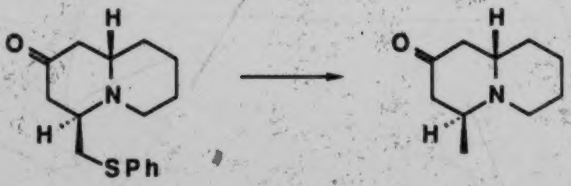
(cis)-4-[(Phenylthio)methyl]octahydro-2*H*-quinolizidin-2-one (211a) and 1-(butyl)-2-[(phenylthio)methyl]-2,3-dihydropyridin-4-one (211b)..



The general procedure for radical cyclization was followed using selenide **210** (120 mg, 0.279 mmol) in benzene (40 mL), triphenyltin hydride (100 µL, 137 mg, 0.391 mmol) in benzene (10 mL), and AIBN (10 mg, 0.060 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 3:1 ethyl acetate-hexane gave **211a** (30 mg, 39%) as a homogeneous (^{1}H NMR, 400 MHz) oil, as well as non-cyclized reduction product **211b** (39 mg, 51%). The cyclized product **211a** had: FT-IR ($CHCl_3$ cast) 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.40 (m, 2 H), 1.55-1.75 (m, 4,H), 2.99,(d, J = 7.1 Hz, 2 H), 2.53-2.62 (m, 2 H), 2.67-2.81 (m, 4 H), 2.26-3.35 (m, 2 H), 7.20-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.85, 25.71, 31.05, 33.83, 44.41, 47.28, 50.80, 53.93, 61.57, 126.49, 128.97, 129.39, 129.94, 195.40; exact mass, *m/z* calcd for $C_9H_{14}NO$ (M - $CH_2SC_6H_5$) 152.1075, found 152.1075. Compound **211b** had: FT-IR ($CHCl_3$ cast) 1584, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.25-1.37 (m, 2 H), 1.45-1.50 (m, 2 H), 2.65 (dd, J = 14.0, 1 Hz, 1 H), 2.74 (dd, J = 14.0, 6.0 Hz, 1 H), 3.07-3.18 (m, 2

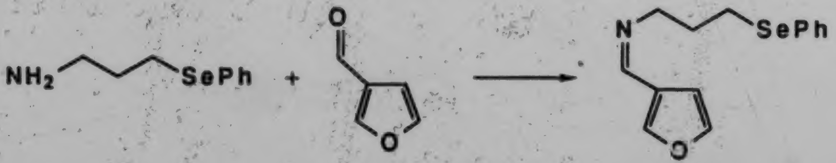
H), 3.22-3.30 (m, 2 H), 3.50-3.57 (m, 1 H), 4.92 (d, J = 7.2 Hz, 1 H), 6.89 (d, J = 7.2 Hz, 1 H), 7.20-7.40 (m, 5 H); exact mass, *m/z* calcd for $C_{16}H_{21}NOS$ 275.1344, found 275.1345.

(*cis*)-4-Methyloctahydro-2*H*-quinolizidin-2-one (myrtine) (212).[76]



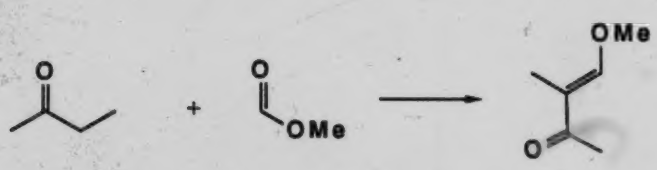
A suspension of Raney nickel in ethanol was added to sulfide **211a**, and the mixture was refluxed for 1 h. The mixture was filtered through Celite and evaporated. The residue (**212**) had identical spectral data as has been reported for the natural product, myrtine.

N-(3-Furylmethylidine)-3-(phenylseleno)propylamine (218).



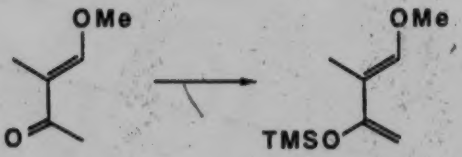
A mixture of amine **204** (58 mg, 0.271 mmol), 3-furaldehyde (26 mg, 0.271 mmol), and $MgSO_4$ (*ca* 100 mg) in ether (2 mL) was stirred at room temperature for 1 h. Filtration, followed by evaporation of the solvent, gave the crude imine in near quantitative yield (^{1}H NMR, 200 MHz), and the material was used without purification. The imine had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85-2.20 (m, 2 H), 3.00 (t, J = 7.2 Hz, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 6.78 (s, 1 H), 7.18-7.78 (m, 7 H), 8.15-8.20 (m, 1 H).

(*E*)-3-Methyl-4-methoxy-3-buten-2-one (219').



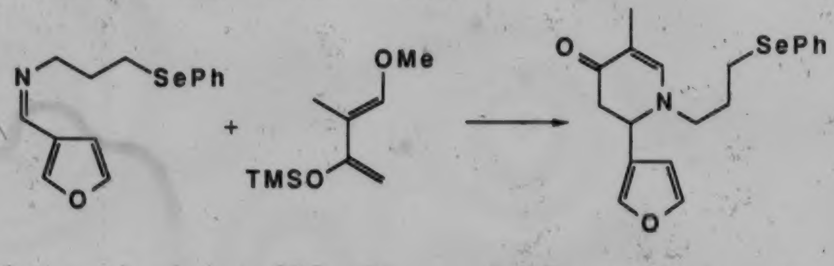
A modified literature procedure was followed.[80] Methyl ethyl ketone was added dropwise over 30 min to a refluxing mixture of sodium hydride (60% in oil, 3.50 g, 91.3 mmol) and methyl formate (4.2 mL) in THF (500 mL). After 1 h, dimethyl sulfate (1.1 eq) was injected, and refluxing was continued for 30 min. At this time, water (15 mL) was added and heating was continued for a further 30 min. The mixture was cooled and diluted with ether (500 mL). The organic phase was washed with aqueous ammonia (2 M, 300 mL), water (300 mL), and brine (300 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm) with 1:3 ethyl acetate-hexane gave **219'** (3.5 g, 34%) as a homogeneous (^{1}H NMR, 80 MHz) oil: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.65 (s, 3 H), 2.25 (s, 3 H), 3.85 (s, 3 H), 7.25 (s, 1 H).

(*E*)-3-Methyl-4-methoxy-2-(trimethylsilyloxy)-1,3-butadiene (219).



Ketone **219'** (2.21 g, 19.36 mmol) was added dropwise to a stirred and cooled (-78°C) solution of LDA [21.39 mmol, from *n*-butyllithium (1.55 M, 13.8 mL, 21.39 mmol) and diisopropylamine (2.17 g, 21.40 mmol)] in THF (30 mL). After 30 min, chlorotrimethylsilane (75% v/v in triethylamine, 5 ml) was added dropwise. After 10 min, the cooling bath was removed, and the mixture was allowed to warm to room temperature over about 1 h. The resulting mixture was diluted with ether (50 mL), and filtered through Floricil, evaporated, and distilled to give diene **219** (2.50 g, 70%): bp 65-70°C (14 mm Hg); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.05-0.35 (m, 9 H), 1.68 (s, 3 H), 3.65 (s, 3 H), 4.14 (s, 1 H), 4.25 (s, 1 H) 6.50 (s, 1 H).

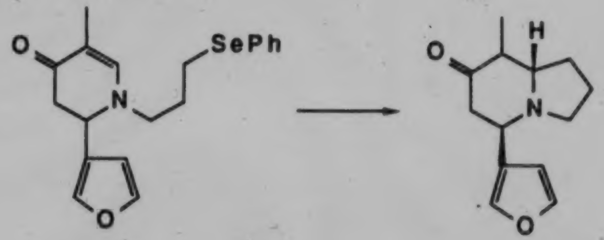
2-(3-Furyl)-5-methyl-1-[3-(phenylseleno)propyl]-2,3-dihydropyridin-4-one (220).



The crude imine **218** (79 mg, 0.271 mmol) in THF (1 mL) was added to a stirred solution of diene **219** (250 mg, 1.340

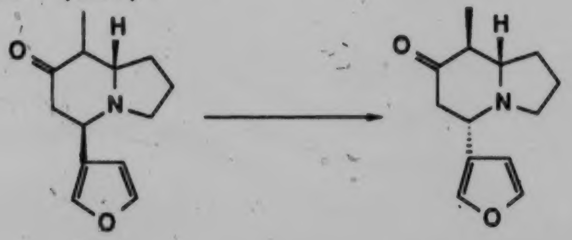
mmol) and zinc chloride (60 mg, 0.440 mmol) in THF (2 mL) at room temperature. After 40 h, the resulting mixture was diluted with ethyl acetate (10 mL), washed with water (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:1 ethyl acetate-hexane gave **220** (73 mg, 72%) as a homogeneous (^1H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1602, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3 H), 1.89 (quintet, J = 7.0 Hz, 2 H), 2.58 (ABq, J = 16.5, 7.5 Hz, 1 H), 2.72 (ABq, J = 16.5, 6.5 Hz, 1 H), 2.77-2.93 (m, 2 H), 3.19 (t, J = 7.0 Hz, 2 H), 4.42 (dd, J = 7.5, 6.5 Hz, 1 H), 6.34, (s, 1 H), 6.85 (s, 1 H), 7.25-7.30 (m, 4 H), 7.37 (s, 1 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.57, 24.26, 29.00, 42.69, 52.30, 52.96, 105.49, 109.03, 123.01, 127.24, 129.15, 132.95, 140.09, 143.71, 151.50, 190.03; exact mass, *m/z* calcd for $C_{19}H_{21}NO_3Se$ 375.0738, found 375.0738.

(5α,8aα)-8-methyl-5-(3-furyl)hexahydro-7(1*H*)-indolizidinone (221).



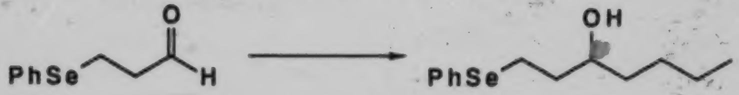
The general procedure for radical cyclization was followed using selenide **220** (93 mg, 0.248 mmol) in benzene (20 mL), triphenyltin hydride (105 µL, 144 mg, 0.411 mmol) in benzene (10 mL), and AIBN (8 mg, 0.048 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 3:2 ethyl acetate-hexane gave **221** (45 mg, 83%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, J = 6.3 Hz, $-CH_3$), 1.54-1.64 (m, C(1)H_e), 1.65-1.75 (m, C(1)H_a), 1.88-2.03 (m, C(3)H_2), 2.34-2.39 (m, C(8)H, C(8a)H), 2.46 (q, J = 8.3 Hz, C(3)H_e), 2.57 (dd, J = 6.5, 2.8 Hz, C(6)H_e), 2.91-3.02 (m, C(6)H_a, C(3)H_a), 4.45 (dd, J = 6.5, 2.3 Hz, C(5)H), 6.70 (s, 1 H), 7.22 (s, 1 H), 7.38 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.52, 21.96, 30.68, 45.35, 49.50, 50.50, 52.01, 61.83, 111.08, 121.53, 140.66, 142.59, 211.33; exact mass, *m/z* calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1258. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.15; H, 7.72; N, 6.53.

(5α,8β,8aβ)-8-methyl-5-(3-furyl)hexahydro-7(1*H*)-indolizidinone (217).[79b]



A literature procedure was followed.[79b] A solution of ketone **221** (50 mg, 0.228 mmol), aqueous sodium hydroxide (2.5 M, 50 µL, 0.125 mmol) in methanol (2 mL) was heated at reflux for 8 h. The mixture was then diluted with ether (20 mL), washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 2:5 ethyl acetate-hexane gave **217** (35 mg, 70%) as a homogeneous (^{1}H NMR, 400 MHz) oil, as well as **221** (5 mg, 10%). Compound **217** had: FT-IR ($CHCl_3$ cast) 1715, 2792 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (d, J = 6.5 Hz, 3 H), 1.60-1.92 (m, 3 H), 1.90-2.10 (m, 3 H), 2.41-2.50 (m, 2 H), 2.72 (ddd, J = 14.0, 11.9, 1.3 Hz, 1 H), 2.95 (td, J = 18.0, 2.0 Hz, 1 H), 3.30 (dd, J = 11.8, 3.3 Hz, 1 H), 6.50, (s, 1 H), 7.37 (s, 1 H), 7.40 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.45, 21.28, 30.30, 48.36, 50.24, 52.02, 57.82, 70.31, 108.86, 126.60, 139.43, 143.37, 209.60.

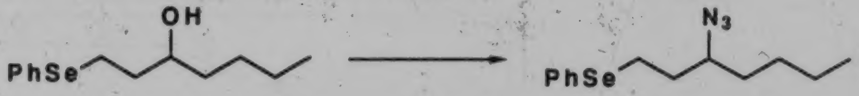
1-(Phenylseleno)-3-heptanol (222).



Aldehyde **176** (1.62 g, 7.58 mmol) in dry THF (10 mL) was added dropwise over 10 min to a stirred and cooled (-78°C) solution of *n*-butyllithium (1.5 M in hexanes, 10.0 mL, 15.0 mmol) in THF (10 mL). After 30 min, the cooling bath was removed, and the reaction was quenched by addition of saturated aqueous ammonium chloride (2 mL) followed by water (15 mL). The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 ethyl acetate-hexane gave **222** (1.62 g, 64%) as a homogeneous (^{1}H NMR, 400

MHz) oil: FT-IR ($CHCl_3$ cast) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.20-1.48 (m, 6 H), 1.75-1.91 (m, 3 H), 2.95-3.10 (m, 2 H), 3.70 (quintet, J = 6.0 Hz, 1 H), 7.17-7.27 (m, 3 H), 7.45-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.96, 22.56, 24.04, 27.65, 37.00, 37.29, 71.34, 126.67, 128.96, 130.17, 132.56; exact mass, *m/z* calcd for $C_{13}H_{20}OSe$ 272.0679, found 272.0676. Anal. Calcd for $C_{13}H_{20}OSe$: C, 57.57; H, 7.43; O, 5.90. Found: C, 57.82; H, 7.29; O, 6.08.

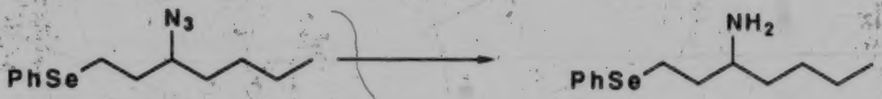
3-Azido-1-(phenylseleno)heptane (223).



A mixture of alcohol **222** (570 mg, 2.101 mmol) and *p*-toluenesulfonyl chloride (480 mg, 2.518 mmol) in pyridine (1 mL), was left to stand at 0°C for 18 h. The resulting mixture was taken up in ether (30 mL), and the organic layer was washed with water (2 x 15 mL), hydrochloric acid (1 M, 15 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. The residue was taken up in dry DMF (10 mL) and sodium azide (270 mg, 4.153 mmol) was added. After stirring for 4 h, the mixture was taken up in ether (50 mL) and the organic layer was washed with water (2 x 20 mL), hydrochloric acid (1 M, 10 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 ethyl acetate-hexane gave **223** (360 mg, 58%) as a homogeneous (^1H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 2095

cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.22-1.45 (m, 4 H), 1.45-1.60 (m, 2 H), 1.83 (q, J = 7.2 Hz, 2 H), 2.90 (dt, J = 12.1, 7.8 Hz, 1 H), 3.02 (ddd, J = 12.1, 7.0, 6.2 Hz, 1 H), 3.41 (quintet, J = 5.3 Hz, 1 H), 7.20-7.30 (m, 3 H), 7.45-7.51 (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 13.88, 22.39, 23.97, 28.06, 33.84, 34.77, 62.42, 126.96, 129.08, 129.67, 132.67; exact mass, *m/z* calcd for $C_{13}H_{19}N_3Se$ 297.0742, found 297.0738. Anal. Calcd for $C_{13}H_{19}N_3Se$: C, 52.88; H, 6.49; N, 14.23. Found: C, 52.78; H, 6.40; N, 13.75.

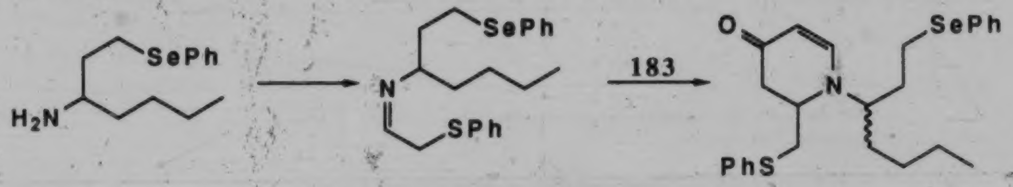
1-(Phenylseleno)-3-heptanamine (224).



Azide **223** (370 mg, 1.253 mmol) in THF (2 mL) was added dropwise to a stirred and cooled (0°C) suspension of lithium aluminum hydride (100 mg, 2.635 mmol) in THF (2 mL). The resulting mixture was allowed to warm to room temperature over a period of about 1 h. At that time, the reaction was quenched by the sequential addition of water (0.1 mL), aqueous sodium hydroxide (15%, 0.1 mL), and water (0.3 mL). The resulting mixture was filtered and washed with ether (20 mL), and the combined washings were dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:19 ethanol-ethyl acetate gave **224** (250 mg, 74%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR (CHCl$_3$ cast) 3380 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.89 (t, J = 7.0

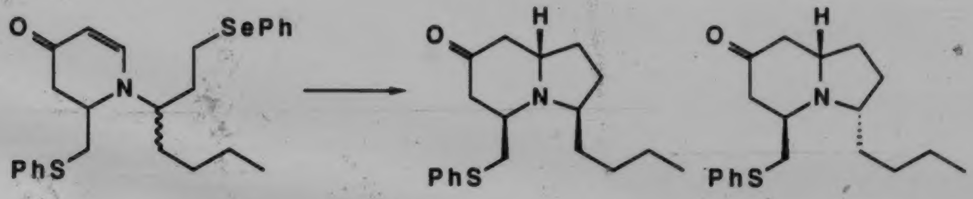
Hz, 3 H), 1.20-1.48 (m, 6 H), 1.60-1.90 (m, 4 H), 1.65 (broad s, 2 H), 2.83 (m, 1 H), 2.91-3.08 (m, 2 H), 7.20-7.30 (m, 3 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.98, 22.66, 24.49, 28.10, 37.43, 37.88, 51.11, 126.65, 128.94, 130.31, 132.42; exact mass, *m/z* calcd for $C_{13}H_{21}NSe$ 271.0839, found 271.0843. Anal. Calcd for $C_{13}H_{21}NSe$: C, 57.77; H, 7.83; N, 5.18. Found: C, 57.67; H, 7.53; N, 5.24.

1-[1-Butyl-3-(phenylseleno)propyl]-2-[(phenylthio)methyl]-2,3-dihydropyridine-3-one (225).



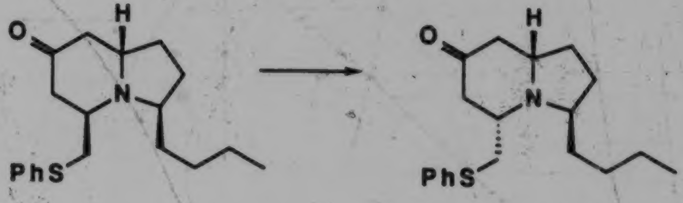
The procedure for compound **220** was followed, using amine **224** (754 mg, 2.790 mmol), (phenylthio)acetaldehyde (425 mg, 2.792 mmol), and $MgSO_4$ (*ca* 200 mg) in ether (4 mL). The ^{1}H NMR (80 MHz) spectrum of the crude product indicated that imine **224'** had formed and this crude material was used without purification, according to the procedure for **206**. Imine **224'** was taken up in dry THF (15 mL) and a solution of diene **183** (1.400 g, 8.125 mmol) and zinc cloride (380 mg, 2.788 mmol) in THF (15 mL) was added. After 48 h, the reaction was quenched by addition of water (20 mL), and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 3:1 ethyl acetate-hexane gave **225** (510 mg, 39% from amine **224**) as a mixture of diastereomers (^{1}H NMR, 400 MHz): FT-IR ($CHCl_3$ cast) 1578, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.0 Hz, 1.5 H), 0.91 (t, J = 7.1 Hz, 1.5 H), 1.10-1.45 (m, 5.5 H), 1.47-1.59 (m, 0.5 H), 1.65-1.85 (m, 1 H), 1.86-1.95 (m, 1 H), 2.60-2.95 (m, 4 H), 3.05-3.25 (m, 3 H), 3.35-3.50 (m, 1 H), 4.94 (d J = 7.8 Hz, 0.5 H), 4.97 (d J = 7.8 Hz, 0.5 H), 6.86 (d J = 7.8 Hz, 0.5 H), 6.88 (d J = 7.8 Hz, 0.5 H), 7.20-7.52 (m, 9 H), 7.45-7.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.83, 22.28, 22.34, 23.87, 24.30, 27.99, 28.71, 33.16, 33.46, 33.53, 34.82, 35.41, 37.85, 37.99, 55.68, 56.27, 63.30, 63.58, 97.69, 97.80, 126.99, 127.37, 127.42, 128.96, 129.13, 129.20, 130.33, 130.50, 133.02, 133.08, 148.27, 148.48, 189.59; exact mass, *m/z* calcd for $C_{25}H_{31}NOSSe$ 473.1292, found 473.1291. Anal. Calcd for $C_{25}H_{31}NOSSe$: C, 63.54; H, 6.61; N, 2.96; S, 6.79. Found: C, 63.39; H, 6.78; N, 2.91; S, 6.73.

(3α,5α,8aα)-3-Butyl-5-[(phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone (226a) and (3α,5β,8aβ)-3-Butyl-5-[(phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone (226b).



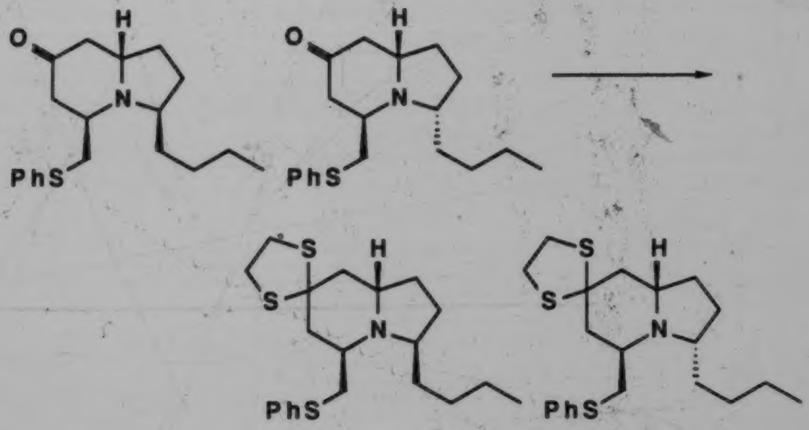
The general procedure for radical cyclization was followed using selenides **225** (67 mg, 0.142 mmol) in benzene (14 mL), triphenyltin hydride (55 μL, 76 mg, 0.215 mmol) in benzene (10 mL), and AIBN (5 mg, 0.030 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:4 ethyl acetate-hexane gave a mixture (^{1}H NMR, 400 MHz) of **226a** and **226b** (35 mg, 78%): FT-IR ($CHCl_3$ cast) 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 6.8 Hz, 1.5 H), 0.90 (t, J = 6.8 Hz, 1.5 H), 1.00-1.65 (m, 8 H), 1.80-1.95 (m, 1 H), 2.00-2.14 (m, 1.5 H), 2.15-2.27 (m, 1 H), 2.36 (dt, J = 13.5, 1 Hz, 0.5 H), 2.49 (dt, J = 13.5, 1.3 Hz, 0.5 H), 2.54 (dd, J = 13.0, 10.0 Hz, 0.5 H), 2.58 (ABq, J = 14.4, 6.2 Hz, 0.5 H), 2.66 (ABq, J = 13.4, 6.2 Hz, 0.5 H), 2.58-2.77 (m, 1 H), 2.86 (dd, J = 13.0, 7.5 Hz, 0.5 H), 2.90-3.05 (m, 1 H), 3.10-3.20 (m, 1 H), 3.45-3.50 (m, 0.5 H), 3.56-3.66 (m, 1 H), 7.12-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.07, 22.93, 22.95, 27.89, 28.03, 28.20, 29.13, 29.57, 29.95, 30.16, 33.47, 35.34, 38.43, 39.96, 44.31, 44.58, 48.28, 52.26, 56.29, 56.38, 57.62, 58.02, 59.03, 125.79, 126.60, 128.78, 128.92, 128.99, 130.20, 135.54, 136.52, 209.83; exact mass, *m/z* calcd for $C_{12}H_{20}NO$ (M - $CH_2SC_6H_5$) 194.1545, found 194.1545. Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41; S, 10.10. Found: C, 71.60; H, 8.55; N, 4.88; S, 9.95.

(3α,5β,8aα)-3-Butyl-5-[(phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone (226c).



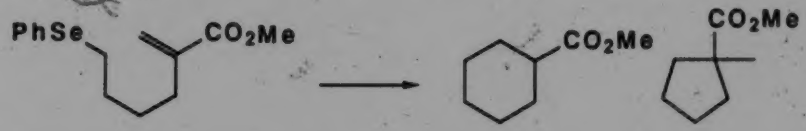
The procedure for compound **221** was followed, using the indolizidines **226a** and **226b** (30 mg, 0.096 mmol) and aqueous sodium hydroxide (10%, 50 μL), in methanol (2 mL). The mixture was refluxed for 30 h. The solution was diluted with water (5 mL) and extracted with ether (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:7 ethyl acetate-hexane gave **226c** (7 mg, 23%) as well as recovered **226a** and **226b** (20 mg, 67%). Compound **226c** had: FT-IR ($CHCl_3$ cast) 1720, 2805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 0.95-1.35 (m, 6 H), 1.45-1.65 (m, 2 H), 1.95-2.10 (m, 2 H), 2.24 (dd, J = 12.0, 14.0 Hz, 1 H), 2.42-2.51 (m, 2 H), 2.62 (dt, J = 14.9, 2.6 Hz, 1 H), 2.77-2.87 (m, 1 H), 3.00-3.21 (m, 3 H), 3.30-3.38 (m, 1 H), 7.17-7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.12, 22.84, 25.72, 27.14, 28.97, 29.79, 39.01, 45.17, 48.15, 53.90, 58.01, 58.32, 126.51, 128.98, 130.21, 209.08.

(3α,5α,8aα)-3-Butyl-5-[(phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone, cyclic 1,2-ethanediyl thioacetal (227a) and (3α,5β,8aβ)-3-Butyl-5-[(phenylthio)methyl]hexahydro-7(1*H*)-indolizidinone, cyclic 1,2-ethanediyl thioacetal (227b).



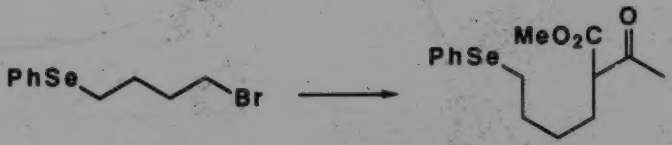
A general literature procedure was followed.[86] Borontrifluoride etherate (50 μL, 59 mg, 0.409 mmol) was added dropwise to stirred and cooled (0°C) solution of ketones **226a** and **226b** (190 mg, 0.604 mmol) and ethanedithiol (100 mg, 1.062 mmol) in dichloromethane (0.5 mL). The cooling bath was removed and stirring was continued for 3 h. The mixture was taken up in ether (20 mL), and the organic layer was washed with aqueous sodium hydroxide (5%, 10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:25 ethyl acetate-hexane gave **227a** (65 mg, 27%), and **227b** (66 mg, 28%), as a well recovered **226a** and **226b** (40 mg, 21%). Compound **227a** had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 0.95-1.08 (m, 1 H), 1.10-1.40 (m, 6 H), 1.41-1.53 (m, 1 H), 1.75-1.87 (m, 3 H), 2.24-2.30 (m, 2 H), 2.74 (dt, J = 14.0, 2.0 Hz, 1 H), 2.74-2.83 (m, 2 H), 3.16 (dd, J = 12.5, 3.2 Hz, 1 H), 3.20-3.44 (m, 6 H), 7.24-7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.10, 23.01, 28.29, 28.36, 28.56, 28.85, 32.87, 37.31, 39.94, 41.41, 49.20, 52.43, 55.55, 58.03, 65.09, 126.07, 128.85, 129.56, 136.63; exact mass, *m/z* calcd for $C_{14}H_{24}NS_2$ (M - $CH_2SC_6H_5$) 270.1350, found 270.1352. Compound **227b** had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.09-1.35 (m, 5 H), 1.36-1.52 (m, 3 H), 1.76 (ABq, J = 12.6, 4 Hz, 1 H), 1.82 (ABq, J = 12.6, 11.0 Hz, 1 H), 1.89-2.00 (m, 2 H), 2.20-2.30 (m, 2 H), 2.25-2.35 (m, 1 H), 3.11-3.20 (m, 1 H), 3.21-3.48 (m, 7 H), 7.20-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.09, 22.98, 28.30, 28.81, 28.93, 35.51, 35.65, 37.39, 38.04, 39.94, 42.62, 53.29, 55.10, 58.75, 65.19, 125.43, 128.71, 137.08; exact mass, *m/z* calcd for $C_{14}H_{24}NS_2$ (M - $CH_2SC_6H_5$) 270.1350, found 270.1352.

Cyclization of 170.



The general procedure for radical cyclization was followed using selenide **170** (90 mg, 0.303 mmol) in benzene (30 mL), triphenyltin hydride (120 μL, 165 mg, 0.470 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Kugelrohr distillation [90°C (15 mm Hg)] of the crude product gave a mixture of two compounds (40 mg, 93%) in a ratio of 7:1 (g.c. analysis), the major one being methyl cyclohexanecarboxylate and the minor, methyl 1-methylcyclopentanecarboxylate as determined by comparison (^{1}H NMR, 400 MHz) with authentic samples.

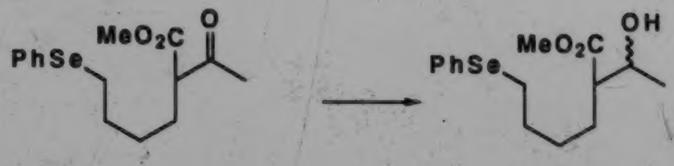
Methyl 3-Oxo-2-[4-(phenylseleno)butyl]butanoate (229).



The procedure used for compound **169** was followed using methyl acetoacetate (200 mg, 1.722 mmol), sodium hydride (60% in oil, 70 mg, 1.750 mmol) in THF (15 mL) and bromide **168** (500 mg, 1.722 mmol). Flash chromatography of the crude product over silica gel (2 x 15 cm) with 1:8 ethyl acetate-hexane gave **229** (370 mg, 66%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 1715, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (quintet, J = 7.5 Hz, 2 H), 1.71 (quintet, J = 7.5 Hz, 2 H), 1.80-1.89 (m, 2 H), 2.20 (s, 3 H), 2.89 (t, J = 7.3 Hz, 2 H), 3.40 (t, J = 7.4 Hz, 1 H), 3.72 (s, 3 H), 7.20-7.29 (m, 3 H), 7.45-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.35, 27.45, 27.55, 28.83, 29.76, 52.34, 59.42, 126.78, 129.00, 130.21, 132.62, 170.15, 202.80; exact mass, *m/z* calcd for $C_{15}H_{20}O_3Se$ 328.0576, found 328.0578. Anal.

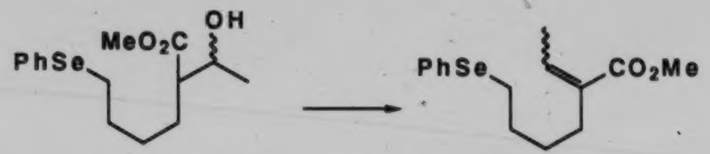
Calcd for $C_{15}H_{20}O_3Se$: C, 55.05; H, 6.16; O, 14.67. Found: C, 54.93; H, 6.29; O, 14.83.

Methyl 3-Hydroxy-2-[4-(phenylseleno)butyl]butanoate (230).



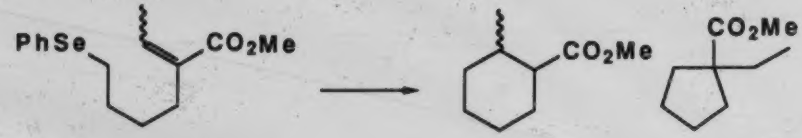
Sodium borohydride (50 mg, 1.322 mmol) was added over 10 min, to a cooled (0°C) solution of compound **229** (350 mg, 1.070 mmol) in absolute ethanol (5 mL). After 5 min, the reaction was quenched by addition of water (10 mL) and the mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated to give **230** as a mixture (^1H NMR, 400 MHz) of isomers that was used without further purification. The crude material could be purified by flash chromatography over silica gel with 1:3 ethyl acetate-hexane to give an inseparable mixture (^1H NMR, 400 MHz) of alcohols **230**: FT-IR ($CHCl_3$ cast) 1734, 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, J = 6.0 Hz, 1.9 H), 1.22 (t, J = 6.0 Hz, 1.1 H), 1.20-1.80 (m, 6 H), 2.30-2.60 (m, 2 H), 2.90 (t, J = 7.5 Hz, 2 H), 3.69 (s, 1.1 H), 3.71 (s, 1.9 H), 3.70-4.25 (m, 1 H), 7.20-7.29 (m, 3 H), 7.40-7.52 (m, 2 H); exact mass, *m/z* calcd for $C_{15}H_{22}O_3Se$ 330.0735, found 330.0735.

Methyl (*E*)- and (*Z*)-2-[4-(Phenylseleno)butyl]-2-butenoate (231).



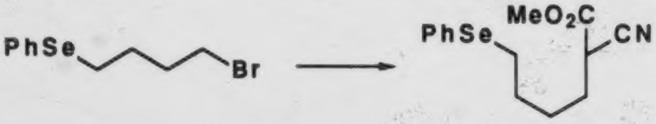
A mixture of crude alcohols **230** (obtained from the previous experiment (*ca* 350 mg, 1.070 mmol), pyridine, (0.5 mL), and *p*-toluenesulfonyl chloride (200 mg, 1.049 mmol) was let stand at 0°C for 16 h. The resulting mixture was taken up in ether (25 mL), washed with water (10 mL), hydrochloric acid (1 M, 10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.5 mL) was added to the residue and, after 30 min at room temperature, the resulting mixture was taken up in ether (15 mL), washed with water (5 mL), hydrochloric acid (1 M, 5 mL), brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 2:25 ethyl acetate-hexane gave **231** (160 mg, 48% from **229**) as a mixture (^{1}H NMR, 400 MHz) of *E* and *Z* isomers in a ratio of 2:1: FT-IR ($CHCl_3$ cast) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.56 (m, 2 H), 1.65-1.75 (m, 2 H), 1.78 (d, J = 7.2 Hz, 1.9 H), 1.94 (d, J = 7.2 Hz, 1.1 H), 2.22 (t, J = 7.5 Hz, 0.8 H), 2.30 (t, J = 7.7 Hz, 1.2 H), 2.88-2.92 (m, 2 H), 3.71 (s, 1.9 H), 3.73 (s, 1.1 H), 5.96 (q, J = 7.2 Hz, 0.4 H), 6.84 (q, J = 7.2 Hz, 0.6 H), 7.20-7.29 (m, 3 H), 7.45-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.21, 15.64, 25.76, 27.57, 27.59, 29.03, 29.14, 29.52, 29.87, 33.88, 51.09, 51.53, 126.61, 126.63, 128.92, 130.40, 130.44, 132.31, 132.44, 132.52, 132.78, 136.72, 137.63, 168.15, 168.40; exact mass, *m/z* calcd for $C_{15}H_{20}O_2Se$ 312.0623, found 312.0631. Anal. Calcd for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.48; O, 10.28. Found: C, 58.08; H, 6.60; O, 9.79.

Cyclization of 231.



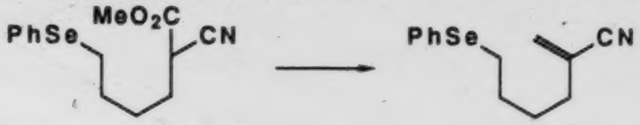
The general procedure for radical cyclization was followed using selenides **231** (60 mg, 0.193 mmol) in benzene (20 mL), triphenyltin hydride (75 µL, 103 mg, 0.294 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Kugelrhor distillation [100°C (15 mm Hg)] of the crude product gave a mixture of two compounds (27 mg, 90%) in a ratio of 3:1 (g.c. analysis). The major compound was methyl 1-ethylcyclopentanecarboxylate and the minor, methyl 2-methylcyclohexanecarboxylate as determined by comparison (^1H NMR, 400 MHz) with authentic samples.

Methyl 2-Cyano-6-(phenylseleno)hexanoate (232).



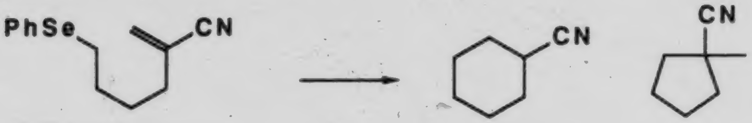
The procedure for compound **169** was followed using methyl cyanoacetate (160 mg, 1.615 mmol), sodium hydride (60% in oil, 63 g, 1.575 mmol) in THF (10 mL) and bromide **168** (245 mg, 0.848 mmol). The reaction was quenched by addition of water (10 mL) and the mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:10 ethyl acetate-hexane gave **232** (160 mg, 62%): FT-IR ($CHCl_3$ cast) 1749, 2315 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56-1.67 (m, 2 H), 1.74 (quintet, J = 7.3 Hz, 2 H), 1.93 (q, J = 7.7 Hz, 2 H), 2.90 (t, J = 7.3 Hz, 2 H), 3.48 (t, J = 7.0 Hz, 1 H), 3.70 (s, 3 H), 7.20-7.30 (m, 3 H), 7.45-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.73, 26.95, 29.15, 37.10, 53.36, 116.18, 126.83, 128.98, 129.82, 132.61, 166.36; exact mass, *m/z* calcd for $C_{14}H_{17}NO_2Se$ 311.0424, found 311.0427. Anal. Calcd for $C_{14}H_{17}NO_2Se$: C, 54.20; H, 5.52; N, 4.51; O, 10.31. Found: C, 53.92; H, 5.67; N, 4.51; O, 10.59.

2-[4-(Phenylseleno)butyl]-2-propenenitrile (233).



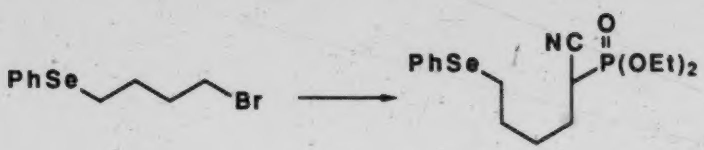
The procedure used for compound **170** was followed using **232** (155 mg, 0.500 mmol) and potassium hydroxide (85%, 39 mg, 0.590 mmol) in methanol (2 mL). The resulting acid was treated with diethylamine (50 mg, 0.683 mmol) and 37% aqueous formaldehyde (50 mg, 0.638 mmol) in 1:1 methanol-water (2 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 2:25 ethyl acetate-hexane gave **233** (60 mg, 45%) as a homogeneous (^{1}H NMR, 400 MHz) oil: FT-IR ($CHCl_3$ cast) 2300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.64-1.77 (m, 4 H), 2.25 (t, J = 7.0 Hz, 2 H), 2.92 (t, J = 6.9 Hz, 2 H), 5.68 (s, 1 H), 5.82 (s, 1 H), 7.20-7.30 (m, 3 H), 7.46-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.16, 27.50, 29.03, 33.99, 118.49, 122.75, 126.86, 129.04, 130.04, 130.40, 132.64; exact mass, *m/z* calcd for $C_{13}H_{15}NSe$ 265.0370, found 265.0370. Anal. Calcd for $C_{13}H_{15}NSe$: C, 59.09; H, 5.72; N, 5.30. Found: C, 59.03; H, 5.84; N, 5.24.

Cyclization of 233.



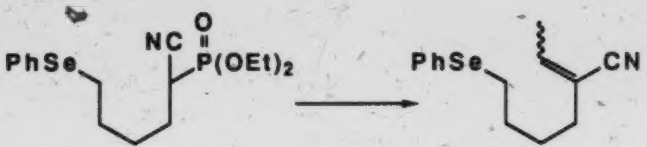
The general procedure for radical cyclization was followed using selenide **233** (32 mg, 0.121 mmol) in benzene (15 mL), triphenyltin hydride (47 µL, 65 mg, 0.184 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Kugelrhor distillation [85°C (15 mm Hg)] of the crude product gave one major (g.c. analysis) compound (27 mg, 90%). The structure was determined to be cyanocyclohexane by comparison (^{1}H NMR, 400 MHz) with an authentic sample. A trace amount of another compound was detected (<5%, g.c., ^{1}H NMR, 400 MHz), which presumably is methyl 1-ethylcyclopentanecarboxylate.

2-(Diethylphosphono)-6-(phenylseleno)hexanenitrile (234).



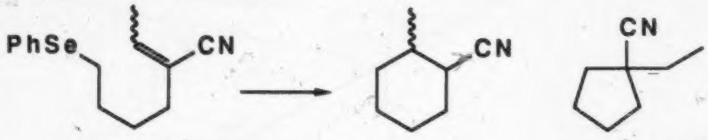
A solution of (diethylphosphono)acetonitrile (242 mg, 1.372 mmol) in THF (2 mL) was added dropwise to a stirred and cooled (0°C) suspension of sodium hydride (60% in oil, 52 mg, 1.356 mmol) in THF (8 mL). After about 10 min, a solution of bromide **168** (400 mg, 1.369 mmol) in THF (3 ml) was added. The resulting mixture was allowed to warm to room temperature, refluxed for 2 h, and then cooled. The reaction was quenched by addition of water (10 mL) and the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 1:10 ethyl acetate-hexane gave **234** (252 mg, 47%): FT-IR ($CHCl_3$ cast) 2250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 7.0 Hz, 6 H), 1.55-1.96 (m, 6 H), 2.80-2.96 (m, 3 H), 4.17-4.29 (m, 4 H), 7.20-7.30 (m, 3 H), 7.45-7.52 (m, 2 H); exact mass, *m/z* calcd for $C_{16}H_{24}NO_3PSe$ 389.0659, found 389.0662.

(*E*)- and (*Z*)-2-[4-(Phenylseleno)butyl]-2-butenenitrile (235).



The procedure for compound **155** was followed using **234** (185 mg, 0.477 mmol), potassium *tert*-butoxide (54 mg, 0.482 mmol) in THF (3 mL), and acetaldehyde (25 mg, 0.567 mmol), in THF (1 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:9 ethyl acetate-hexane gave **235** (75 mg, 57%) as a 3:1 mixture (^{1}H NMR, 400 MHz) of *E* and *Z* isomers: FT-IR (CHCl$_3$ cast) 2214 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.60-1.80 (m, 4 H), 1.76 (d, J = 7.0 Hz, 0.8 H), 1.95 (dt, J = 7.0, 1.6 Hz, 2.2 H), 2.16-2.22 (m, 2 H), 2.87-2.94 (m, 2 H), 6.16 (qt, J = 7.0, 1.6 Hz, 0.7 H), 6.41 (qt, J = 7.0, 1.1 Hz, 0.3 H), 7.20-7.30 (m, 3 H), 7.46-7.51 (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 14.24, 17.01, 27.21, 27.56, 27.79, 27.99, 29.02, 29.25, 33.50, 115.22, 117.40, 126.77, 128.99, 130.10, 132.57, 132.61 142.62, 142.89; exact mass, *m/z* calcd for $C_{14}H_{17}NSe$ 279.0527, found 279.0527.

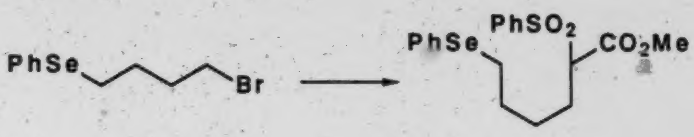
Cyclization of 235.



The general procedure for radical cyclization was followed using selenide **235** (63 mg, 0.226 mmol) in benzene

(20 mL), triphenyltin hydride (87 µL, 97 mg, 0.341 mmol) in benzene (10 mL), and AIBN (10 mg, 0.06 mmol) in benzene (10 mL). Kugelrohr distillation [90°C (15 mm Hg)] of the crude product gave a mixture of compounds (25 mg, 87%) determined (g.c., ^{1}H NMR, 400 MHz) to be 2-methylcyanocyclohexanes, 1-ethylcyanocyclopentane, and reduction product (2-butyl-2-butenenitrile) in a ratio of 5:2:1.

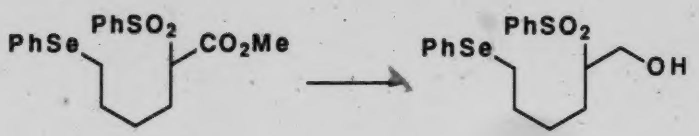
Methyl 6-(Phenylseleno)-2-(phenylsulphonyl)-hexanoate (236).



The procedure for compound **169** was followed using methyl (phenylsulphonyl)acetate[87] (600 mg, 2.806 mmol), sodium hydride (60% in oil, 90 mg, 2.250 mmol) in THF (20 mL) and bromide **168** (395 mg, 1.352 mmol). The reaction was quenched by addition of water (15 mL) and the resulting mixture was extracted with ether (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:15 ethyl acetate-hexane gave **236** (370 mg, 64%): FT-IR ($CHCl_3$ cast) 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (quintet, J = 7.7 Hz, 2 H), 1.68 (quintet, J = 7.5 Hz, 2 H), 1.90-2.06 (m, 2 H), 2.79-2.90 (m, 2 H), 3.64 (s, 3 H), 3.92, (dd, J = 11.0, 4.4 Hz, 1 H), 7.20-7.28 (m, 3 H), 7.42-7.47 (m, 2 H), 7.56 (t, J = 7.8 Hz, 2 H), 7.68 (tt,

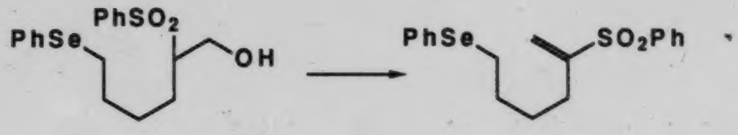
J = 7.5, 1.0 Hz, 1 H), 7.85 (dd, J = 7.8, 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.06, 26.79, 26.95, 29.32, 52.82, 60.67, 126.76, 128.35, 128.95, 129.11, 129.84, 132.49, 134.21, 136.85, 166.17; exact mass, *m/z* calcd for $C_{19}H_{22}O_4SSe$ 426.0404, found 426.0397. Anal. Calcd for $C_{19}H_{22}O_4SSe$: C, 53.64; H, 5.21; O, 15.04; S, 7.54. Found: C, 53.49; H, 5.20; O, 14.72; S, 7.58.

6-(Phenylseleno)-2-(phenylsulphonyl)-1-hexanol (237).



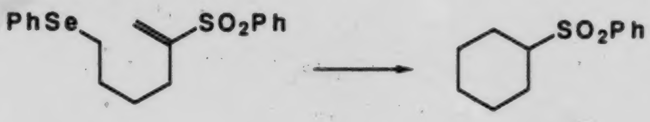
Compound **236** (175 mg, 0.411 mmol) in THF (2 mL), was added to a stirred and cooled (0°C) suspension of lithium aluminum hydride in THF (1 mL). After 30 min, the reaction was quenched by the sequential addition of water (0.025 mL), aqueous sodium hydroxide (15%, 25 µL), and water (75 µL). The mixture was filtered and evaporation of the solvent gave **237** as a homogeneous (tlc) oil that could be used in the next step without purification. Flash chromatography over silica gel (2 x 15 cm) with 1:2 ethyl acetate-hexane provided pure (^{1}H NMR, 400 MHz) **237**: FT-IR ($CHCl_3$ cast) 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30-1.85 (m, 7 H), 2.70-2.95 (m, 2 H), 2.99-3.11 (m, 1 H), 3.80-4.00 (m, 2 H), 7.20-7.30 (m, 3 H), 7.40-7.74 (m, 5 H), 7.85-7.96 (m, 2 H); exact mass, *m/z* calcd for $C_{18}H_{22}O_3SSe$ 398.0455, found 398.0460.

6-(Phenylseleno)-2-(phenylsulphonyl)-1-hexene (238).



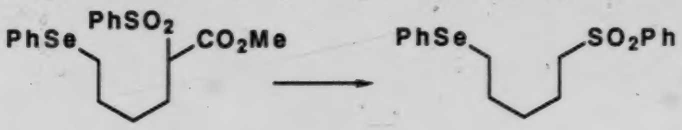
The alcohol **237** obtained from the previous experiment was treated according to the procedure for compound **231**, using *p*-toluenesulfonyl chloride (90 mg, 0.472 mmol) in pyridine (0.3 mL). The crude tosylate was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave **238** (85 mg, 55% from **236**) as a homogeneous (^{1}H NMR, 400 MHz) oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.70 (m, 4 H), 2.22 (t, J = 7.0 Hz, 2 H), 2.81 (t, J = 6.9 Hz, 2 H), 5.70 (s, 1 H), 6.35 (s, 1 H), 7.20-7.30 (m, 3 H), 7.41-7.47 (m, 2 H), 7.53 (t, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.86 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.18, 27.46, 28.54, 29.19, 123.22, 126.81, 128.20, 129.01, 129.16, 130.06, 132.54, 133.46, 138.78, 150.12; exact mass, *m/z* calcd for $C_{18}H_{20}O_2SSe$ 380.0347, found 380.0350. Anal. Calcd for $C_{18}H_{20}O_2SSe$: C, 56.9[illegible] H, 5.31; O, 8.43; S, 8.45. Found: C, 57.05; H, 5.34; O, 8.04; S, 8.70.

Cyclization of 238.



The general procedure for radical cyclization was followed using selenide **238** (28 mg, 0.074 mmol) in benzene (7 mL), triphenyltin hydride (20 µL, 27 mg, 0.074 mmol) in benzene (5 mL), and AIBN (3 mg, 0.018 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave (phenylsulfonyl)cyclohexane (14 mg, 84%) whose structure was confirmed by comparison with an authentic sample: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.05-1.29 (m, 3 H), 1.42 (qd, J = 12.3, 4.2, Hz, 2 H), 1.63-1.71 (m, 1 H), 1.81 (m, 2 H), 2.07 (d, J = 13.1 Hz, 2 H), 2.92 (tt, J = 12.1, 6.9 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 2 H), 7.76 (t, J = 7.2 Hz, 1 H), 7.87 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 23.42, 25.06, 25.48, 63.46, 128.97, 128.99, 133.46, 137.34; exact mass, *m/z* calcd for C_6H_{11} (M - $C_6H_5SO_2$) 83.0861, found 83.0865.

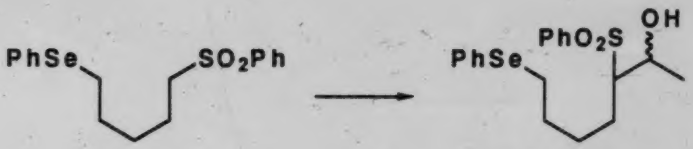
1-(Phenylseleno)-5-(phenylsuphonyl)pentane (239).



A general literature procedure was followed.[51] A mixture of compound **236** (504, mg, 1.185 mmol) and sodium cyanide (90 mg, 1.876 mmol) in DMSO (4 mL) was heated at 90°C for 4 h. Water (100 mL) was added, the mixture extracted with ether, and the combined organic extracts were washed with brine, dried (MgSO$_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:4

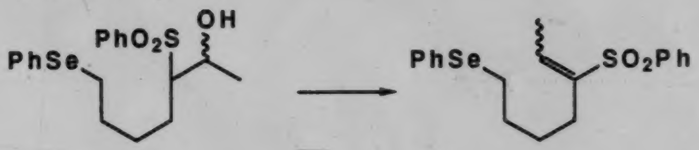
ethyl acetate-hexane gave **239** (380 mg, 87%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (quintet, J = 6.0 Hz, 2 H), 1.60-1.75 (m, 4 H), 2.85 (t, J = 7.1 Hz, 2 H), 3.05 (t, J = 8.0 Hz, 2 H), 7.20-7.30 (m, 3 H), 7.40-7.50 (m, 2 H), 7.58 (t, J = 7.4 Hz, 2 H), 7.76 (tt, J = 7.2, 1.0 Hz, 1 H), 7.90 (d, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.12, 27.19, 28.25, 29.45, 56.03, 126.85, 128.00, 129.04, 129.26, 130.02, 132.57, 133.66, 139.10; exact mass, *m/z* calcd for $C_{17}H_{20}O_2SSe$ 368.0350, found 368.0349. Anal. Calcd for $C_{17}H_{20}O_2SSe$: C, 55.58; H, 5.49; O, 8.71; S, 8.73. Found: C, 55.29; H, 5.51; O, 8.83; S, 8.96.

7-(Phenylseleno)-3-(phenylsuphonyl)-2-heptanol (240).



n-Butyllithium (1.6 M in hexanes, 0.53 mL, 0.885 mmol) was added dropwise to a stirred and cooled (-78°C) solution of **239** (293 mg, 0.798 mmol) in THF (10 mL). After 15 min, a solution of acetaldehyde (36 mg, 0.817 mmol) in THF (1 mL) was added. The cooling bath was removed and after 30 min, the reaction was quenched by the addition of water (10 mL) and the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **240** as an apparently homogeneous (tlc) oil that was used in the next step without purification. Compounds **240** could be purified by flash chromatography over silica gel (2 x 15 cm) with 1:2 ethyl acetate-hexane. The alcohols **240** had: FT-IR ($CHCl_3$ cast) 3460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6.8 Hz, 2 H), 1.31 (d, J = 6.2 Hz, 1 H), 1.30-1.95 (m, 6 H), 2.75-2.9 (m, 2.7 H), 3.03 (q, J = 6.2 Hz, 0.3 H), 3.18 (d, J = 3.5 Hz, 0.7 H), 3.39 (d, J = 3.7 Hz, 0.3 H), 4.20-4.40 (m, 1 H), 7.20-7.30 (m, 3 H), 7.40-7.50 (m, 2 H), 7.50-7.75 (m, 3 H), 7.76-7.92 (m, 2 H); exact mass, *m/z* calcd for $C_{19}H_{24}O_3SSe$ 412.0612, found 412.0644.

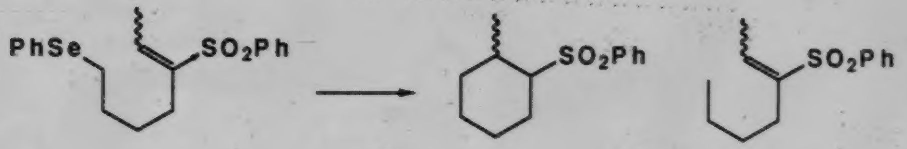
(*E*)- and (*Z*)-7-(Phenylseleno)-3-(phenylsulfonyl)-2-hexene (241).



The crude alcohols **240** obtained from the previous experiment were treated according to the procedure for compound **231** using *p*-toluenesulfonyl chloride (160 mg, 0.839 mmol) in pyridine (0.5 mL). The crude tosylate was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave **241** (105 mg, 33% from **239**) as a mixture of *E* and *Z* isomers in an approximate ratio of 1:1: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (quintet, J = 6.0 Hz, 2 H), 1.56-1.75 (m, 4 H), 1.82 (d, J = 7.1 Hz, 1.5 H), 2.1

(d, J = 7.3 Hz, 1.5 H), 2.21 (t, J = 8.0 Hz, 1 H), 2.29 (t, J = 7.0 Hz, 1 H), 2.79 (t, J = 7.5 Hz, 1 H), 2.84 (t, J = 7.0 Hz, 1 H), 6.10 (q, J = 7.3 Hz, 0.5 H), 6.99 (q, J = 7.1 Hz, 0.5 H), 7.20-7.30 (m, 3 H), 7.40-7.50 (m, 2 H), 7.50-7.56 (m, 2 H), 7.56-7.61 (m, 1 H), 7.80-7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.09, 14.82, 25.60, 27.08, 27.25, 28.57, 29.04, 29.29, 29.76, 32.40, 126.70, 126.73, 127.09, 127.94, 128.95, 129.01, 130.16, 132.47, 132.52, 133.04, 133.06, 137.34, 137.79, 139.83, 141.00, 142.44, 141.64; exact mass, *m/z* calcd for $C_{19}H_{22}O_2SSe$ 394.0513, found 394.0508. Anal. Calcd for $C_{19}H_{22}O_2SSe$: C, 58.01; H, 5.64; O, 8.13; S, 8.15. Found: C, 57.72; H, 5.78; O, 8.36; S, 8.25.

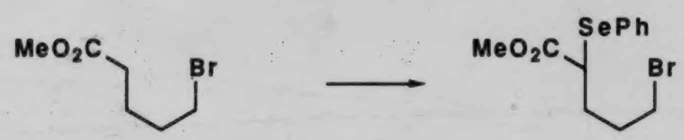
Cyclization of 241.



The general procedure for radical cyclization was followed using selenides **241** (40 mg, 0.102 mmol) in benzene (10 mL), triphenyltin hydride (38 μL, 54 mg, 0.153 mmol) in benzene (10 mL), and AIBN (3 mg, 0.018 mmol) in benzene (10 mL). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:5 ethyl acetate-hexane gave a mixture of two structural isomers (15 mg, 67%) in a ratio of 3:1 (^{1}H NMR, 400 MHz). The major structural isomer was found to be a

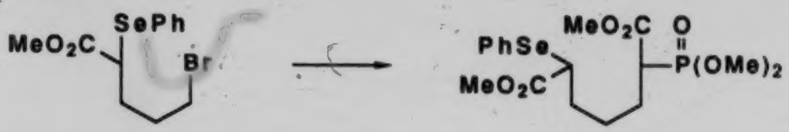
1:1 mixture of *cis* and *trans* 2-methyl(phenylsulfonyl)-cyclohexane as determined by comparison (^{1}H NMR, 400 MHz) with authentic samples, and the minor component was reduced starting material [(*E*)- and (*Z*)-3-(phenylsulfonyl)-2-hexene].

Methyl 5-Bromo-2-(phenylseleno)pentanoate (242).



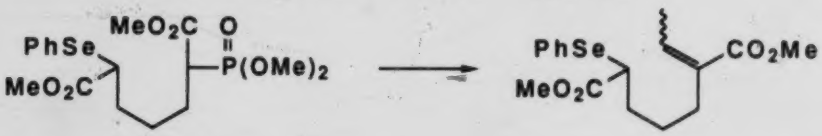
Methyl 5-bromopentanoate (2.0 g, 10.25 mmol) was added dropwise to a stirred and cooled (-78°C) solution of LDA (10.85 mmol) in THF (20 mL). After 20 min, a solution of phenylselenyl chloride (1.96 g, 10.23 mmol) in THF (5 mL) was added. After 10 min, the cooling bath was removed and stirring was continued for 1 h. The resulting mixture was diluted with ether (50 mL), washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 ethyl acetate-hexane gave **242** (1.50 g, 42%): FT-IR ($CHCl_3$ cast) 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70-2.10 (m, 4 H), 3.30-3.40 (m, 2 H), 3.55-3.67 [m (including a singlet at 3.62), 4 H], 7.20-7.45 (m, 4 H), 7.52-7.60 (m, 1 H); exact mass, *m/z* calcd for $C_{12}H_{18}{}^{81}BrO_2Se$ 351.9400, found 351.9401.

Dimethyl 2-(Dimethylphosphono)-6-(phenylseleno)-1.7-heptanedioate (243).



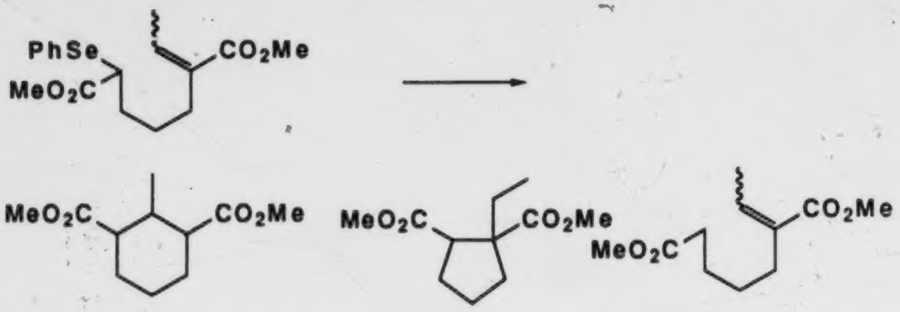
A general literature procedure[57] was followed. Trimethylphosphonoacetate (337 mg, 1.853 mmol) was added dropwise to a solution of sodium hydride (60% in oil, 60 mg, 1.565 mmol) in DMSO (5 mL). After 5 min, bromide **242** (500 mg, 1.428 mmol) in DMSO (1 mL) was added, and the resulting mixture was stirred overnight. The reaction was quenched by addition of water (15 mL) and the mixture was extracted with ethylacetate (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 4:1 ethyl acetate-hexane gave **243** (420 mg, 71%): FT-IR ($CHCl_3$ cast) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30-1.50 (m, 2 H), 1.55-2.05 (m, 4 H), 2.87-3.00 (m, 1 H), 3.35-3.70 (m, 4 H), 3.70-3.85 (m, 6 H), 7.20-7.37 (m, 3 H), 7.55-7.60 (m, 2 H); exact mass, *m/z* calcd for $C_{17}H_{25}O_7PSe$ 452.0503, found 452.0509.

Dimethyl (*E*)- and (*Z*)-2-Ethylidene-6-(phenylseleno)-1,7-heptanedioate (244).



The procedure for **155** was followed using **243** (220 mg, 0.515 mmol), potassium *tert*-butoxide (60 mg, 0.535 mmol), and acetaldehyde (27 mg, 0.613 mmol). Flash chromatography of the crude product over silica gel (1 x 15 cm) with 1:7 ethyl acetate-hexane gave **244** (61 mg, 50%) as a mixture (^{1}H NMR, 400 MHz) of *E* and *Z* isomers in a ratio of 2:1: FT-IR ($CHCl_3$ cast) 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.70 (m, 2 H), 1.85-2.00 (m, 1 H), 1.76 (d, J = 7.0 Hz, 2 H), 1.79 (d, J = 7.2 Hz, 1 H), 2.20-2.50 (m, 3 H), 3.60-3.77 (m, 7 H), 6.86 (q, J = 7.0 Hz, 0.7 H), 6.93 (q, J = 7.2 Hz, 0.3 H), 7.25-7.37 (m, 3 H), 7.55-7.60 (m, 2 H); exact mass, *m/z* calcd for $C_{17}H_{22}O_4Se$ 370.0683, found 370.0677.

Cyclization of 244.



The general procedure for radical cyclization was followed using selenide **245** (45 mg, 0.126 mmol) in benzene (10 mL), triphenyltin hydride (50 µL, 69 mg, 0.196 mmol) in benzene (10 mL), and AIBN (4 mg, 0.018 mmol) in benzene (10 mL). Kugelrohr distillation [60°C (0.3 mm Hg)] of the crude product gave an oil (25 mg, 75%) that was a complex mixture

(^{1}H NMR, 400 MHz, g.c. analysis) of products. The major component was determined to be a mixture of isomeric methyl cyclohexanedicarboxylates, as determined be the appearance of methyl doublets in the ^{1}H NMR spectrum (δ 0.76, J = 6.0 Hz and 0.95, J = 6.0 Hz).

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(83) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (485 mL) and concentrated sulfuric acid (15 mL).

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